

Dynamics of Electrophysiology and Morphology in Older Adults with Age-Related Hearing Loss

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Abstract

Age-related hearing loss (presbycusis) is a highly prevalent disease and can have a severe negative impact on social interactions, and eventually on the quality of life of the people affected. It is therefore of the utmost importance to find biomarkers from which to evaluate presbycusis. Studying presbycusis comprehensively constitutes a complex undertaking because hearing problems are frequently reported by older adults whose hearing impairment has failed to be identified through the traditional assessment of hearing loss, in which such impairment is viewed as a phenomenon occurring at the auditory periphery only. This PhD thesis is among the first to report behavioral consequences and biomarkers of hearing and speech processing problems in older adults which occur independently of peripheral hearing loss.

This PhD thesis provides new insights into auditory perceptual difficulties in older adults and their most common treatment. It extends present frameworks of age-related hearing loss by suitably combining EEG, structural MRI and behavior. The results of the experimental work done in this PhD thesis have several implications: first, novel hearing tests assessing multifactorial aspects of hearing loss, especially central hearing loss, should be implemented in clinics; second, central hearing loss emerges as a function of age-related changes in the morphology and functional lateralization of the auditory areas of the brain; third, peripheral hearing impairment delays central auditory plasticity, which suggests that preventive treatment is the key to understanding speech into old age; and fourth, hearing aids are indispensable for rehabilitation, but clinics need to inform older adults that the hearing aid type and algorithm can only be evaluated after intensive hearing aid usage, across 12 weeks for approximately 12 hours a day. Finally, the fact that hearing aids mainly focus on peripheral hearing treatment points to the necessity for new rehabilitation ideas. It is hoped that the accumulated findings of this PhD thesis will open the door for such novel innovation.

Zusammenfassung

Altersbedingter Hörverlust (Presbyakusis) ist eine hoch prävalente Erkrankung, die sich negativ auf soziale Interaktionen auswirkt und schlussendlich zu einer Abnahme der Lebensqualität von Betroffenen führen kann. Es ist daher äusserst wichtig, Biomarker für Presbyakusis zu definieren, die eine frühe Entdeckung und genaue Diagnose erlauben. Die Erforschung von Presbyakusis ist komplex gestaltet, da ältere Personen sich oft über Hörprobleme beklagen, die aber nicht mit den traditionellen Messmethoden festgestellt werden können, da sie vor allem zur Entdeckung von peripheren Hörschäden entwickelt wurden. Diese Doktorarbeit gehört zu den ersten, die behaviorale und neurophysiologische Konsequenzen von Hör- und Sprachverarbeitungsproblemen bei älteren Personen mit normalem peripheren Hören beschreibt.

Diese Doktorarbeit gibt neue Einblicke in auditorische Verarbeitungsschwierigkeiten bei älteren Personen und deren Behandlung. Sie erweitert bisherige Forschungsansätze zu Presbyakusis, in dem sie EEG, strukturelles MRT und Verhaltenstests in geeigneter Weise kombiniert. Die Resultate dieser experimentellen Arbeit hat verschiedene Implikationen: Erstens, neue Hörtests, die multifaktorielle Aspekte von Hörverlust messen, vor allem zentralen Hörverlust, sollten in Kliniken eingeführt werden; zweitens, zentraler Hörverlust entsteht als Funktion von altersbedingten Veränderungen der Morphologie und der funktionellen Lateralisierung auditorischer Areale im Gehirn; drittens, peripherer Hörverlust verzögert zentrale auditorische Plastizität, was die Bedeutung von präventiven Behandlungen als Unterstützung für Sprachverstehen bis ins hohe Alter hervorhebt; viertens, Hörgeräte sind notwendig für die Rehabilitation von Presbyakusis, aber Kliniken müssen ältere Personen besser informieren, dass man neue Hörgerätetypen und -algorithmen erst nach intensivem Tragen des Högeräts evaluieren kann, nämlich erst nach einer ungefähren Tragezeit von 12 Stunden pro Tag über ungefähr 12 Wochen hinweg. Letztendlich aber ist wichtig, dass neue Rehabilitationsstrategien kreiert werden, denn Hörgeräte fokussieren vor allem auf die Behandlung von peripherem Hörverlust. Die akumulierten Befunde dieser Doktorarbeit sollen die Türen für solche neuen Innovationen öffnen.

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1. General Introduction

1.1. Motivation

“Language, more than anything else, is what makes us human. It appears that no communication system of equivalent power exists elsewhere in the animal kingdom.”

Tecumseh Fitch. *The evolution of language*.

As Tecumseh Fitch describes in his book on the evolution of language, language is a very powerful communication system which is able to convey unlimited sets of concrete and abstract meanings (Fitch, 2005). Language can carry experiences, feelings, and ideas from the present to the past, even expressing what could happen in the future. Because of the importance of language in the human social environment, it is exceptionally hard on many older adults to lose the ability to effortlessly use the auditory modality of human language as they grow older. This occurs because age-related hearing loss (presbycusis) is highly prevalent in old age. In European countries, about 30% of men and 20% of women at the age of 70 years have a hearing loss of 30 decibels (dB) or more (Roth et al., 2011). The practical impact of this is that many enjoyable sounds below a level of 30 dB, such as birds twittering, leaves rustling in the fall, and most importantly some speech sounds cannot be perceived. The high prevalence of presbycusis has also been shown in the US where 58.1% of citizens aged 48-92 years were affected with mild hearing loss that precluded them from perceiving sounds below 40 dB. Furthermore, 30.6% of the same US sample showed moderate hearing loss between >40 and ≤60 dB, and 11.3% experienced marked hearing loss >60 dB (Cruickshanks et al., 1998). This range of hearing loss would almost certainly have prevented these individuals from effortlessly perceiving a great number of speech sounds, such as consonants and vowels. In addition, the prevalence was considerably higher with higher age: 89.5% of individuals older than 80 years suffered from hearing impairment (Cruickshanks et al., 1998).

The fact that the prevalence of presbycusis increases with advancing age (Brant and Fozard, 1990; Cruickshanks et al., 1998; Roth et al., 2011; Wiley et al., 2008) leads to the conclusion that the number of citizens suffering from hearing impairment will

increase drastically in a future of ageing Western societies (Lee et al., 2005; Wiley et al., 2008). For instance, a recent study estimated that a majority of babies born since the year 2000 will live for 100 years or more, on the condition that life expectancy increases at today's pace (Christensen et al., 2009). Naturally, this demographic change brings with it a multitude of serious challenges pertaining to the cost explosion for health care. In this context, it is important to note that presbycusis is already the third most common disease in older adults and has become a severe social and health problem (Mathers et al., 2000), also entailing severe psychosocial problems.

To illustrate these problems, research has revealed that presbycusis makes it difficult to partake in spoken conversations and hence leads to a reduced quality of life (Heinrich et al., 2015; Vannson et al., 2015). The verbal communication difficulties experienced by people with hearing loss can also result in a higher risk of developing depressive symptoms (mainly due to the feeling of being excluded), withdrawal from a wide range of social activities, and social isolation which, in turn, may lead to a poorer quality of life (Arlinger, 2003). In brief, presbycusis can result in profound alterations to the ordinary, daily life of the people affected by this deficit.

For all of these reasons, it is clearly important and relevant to find effective treatments for this disease. To do so, the factors that contribute to the emergence of presbycusis need to be elucidated in order to target its causes preventively. But what is known about how presbycusis emerges? Traditionally, researchers and clinicians studying the causes of presbycusis defined it as age-related damage to the hair cells of the cochlea, and thus as hearing loss occurring at the periphery of the auditory system (peripheral hearing loss) (Humes et al., 2012; Overell and Lindahl, 2004; Pickles, 2012). As the name “age-related hearing loss” implies, aging and its consequences play an essential role in the emergence of this type of peripheral hearing loss. Additionally, studies suggest that noise exposure and genetic vulnerability are also major contributors to the development of presbycusis (Gates and Mills, 2005). Specifically, it seems that the influence of environmental factors increases with age, whereas the influence of genetic factors decreases (Karlsson et al., 1997). It has been observed that this kind of damage to the inner ear first manifests in lower audibility (Lee et al., 2005; Wiley et al., 2008), and was therefore measured by assessing the audibility thresholds of sine wave tones at different frequencies. During such procedures, individuals are

presented with sine wave tones for which the sound pressure level is continuously increased until the participant signals that they are able to perceive the tone. In older adults, a higher audibility threshold typically occurs first in the higher frequencies, which affects speech processing in the way that perceiving fricatives, such as /f/, /sch/, or /s/, is limited (Giroud et al., under review). As soon as the peripheral hearing loss extends to the lower frequencies between 2-4 kHz, which are crucial for understanding voiceless consonants such as /ch/, /f/, /k/, or /p/ and vowels, the perception of speech is generally disrupted (Gates and Mills, 2005; Huang and Tang, 2010a).

These observations notwithstanding, a recent review and opinion paper authored by several leading hearing researchers concluded that speech processing problems as described above do not only evolve because of peripheral cochlear damage, but that the aging brain may play an additional role (Humes et al., 2012). Importantly, this paper suggested that the definition of presbycusis be extended accordingly (Humes et al., 2012). In other words, the ability to hear and to perceive speech is not only a function of the ear, but also of the brain, and aging may also impact the brain structure and functions relevant for the hearing and processing of speech. This broadening of the concept of age-related hearing loss originated from the review of a variety of experiments that observed lower speech understanding performance in older compared to younger adults, this despite their normal peripheral hearing as indicated by age-appropriate audibility thresholds (Fostick et al., 2013; Füllgrabe, 2013; Füllgrabe et al., 2015; Hopkins and Moore, 2011; Humes, 2007). Furthermore, many older adults reported that they could *hear* that someone was speaking and that the level was high enough, but that they did not understand *what* the content of the spoken utterance was (Anderson et al., 2012). Thus, researchers concluded that a high level of an acoustic signal does not necessarily mean that the signal can also be processed and understood by older adults. Such age-related differences in speech perception, despite normal peripheral hearing, have therefore been attributed to the aging brain and correspondingly named “central age-related hearing loss” or “central presbycusis” (Humes et al., 2012). In other words, central presbycusis includes age-related changes of the auditory portions of the central nervous system (brainstem, subcortical and cortical regions) as causes for hearing problems in older adults. Thus, it has been acknowledged that the interaction of peripheral and central auditory, and also cognitive function, is responsible for speech understanding in older adults, and that deficits in speech

processing do not only occur due to peripheral hearing loss (Humes et al., 2012). To give an example, older adults may hear their partner speaking in a restaurant because (s)he is speaking loudly, but the background noise is still relatively difficult to ignore. Thus, this older person needs to be able to selectively attend (cognition) the spoken utterances of the partner and at the same time ignore (cognition) the background noise. Furthermore, this person's auditory brainstem and cortical auditory areas need to be able to process (central auditory functions) the incoming, maybe distorted speech signal (in the case that this person suffers from peripheral hearing loss) and then send this signal to the higher language-relevant brain circuits in order to create meaning out of the message carried in the acoustic signal.

These insights into the emergence of speech processing deficits in older adults have gained increasingly more attention over the last few years, opening up a completely new, interdisciplinary research field, partially referred to as “cognitive hearing science” (Arlinger et al., 2009). This new field unites aspects of neuroscience, hearing research, cognitive psychology, and phonetics. The combined knowledge from each of these disciplines has already led to a more comprehensive description of the causes of speech processing problems in older adults, as described above. On the basis of this comprehensive understanding -- that age-related hearing loss is not only peripheral but also central -- we can only assume that the actual prevalence of age-related hearing loss and its psychosocial consequences and health care costs have to date been grossly underestimated.

At present, there are only few neuroscientific studies that have examined the specific age-related changes of subcortical and cortical structures and function that relate to speech processing differences between younger and older adults. Thus, the motivation behind this PhD thesis was to fill this gap and, as one goal, specifically to address age-related differences in the structure and function of cortical auditory and higher language-relevant circuits, and how these then relate to speech perception in older compared to younger adults with normal peripheral hearing.

Another interest fuelling this thesis was to evaluate the potential benefits and limitations of hearing aids using the broader definition of hearing loss. This question is particularly important because hearing aids, which are currently the most common

treatment for age-related hearing loss, mainly treat peripheral hearing loss by amplifying sounds. As described above, restoration of audibility does not automatically improve speech understanding (Humes, 2007). To complicate this issue, only 10% of individuals with hearing loss who could potentially benefit from a hearing aid actually use one (Gates et al., 1990). The above-mentioned negative consequences may become even more likely, in the event that many older adults remain untreated (Chien and Lin, 2012; Popelka et al., 1998) or do not wear their hearing aids due to limited satisfaction (Bertoli et al., 2009). Recent advancements in hearing aid research have led to the creation of different hearing aid algorithms that may be more beneficial to the hearing impaired than traditional amplification hearing aids. For example, nonlinear frequency compression (NLFC) is a hearing aid feature in which the high-frequency signal, typically lost to the older hearing impaired, is compressed into a lower frequency range (McDermott and Henshall, 2010). NLFC has been reported to improve the recognition of high-frequency consonants, such as fricatives and monosyllabic words (Alexander, 2016; McCreery et al., 2014; Wolfe et al., 2010, 2011, 2015). It is therefore vitally important to explore the role of hearing aids and different hearing aid algorithms in the context of a broader understanding of speech processing in older adults. Moreover, knowledge of the benefits and limitations of hearing aids may enable researchers to create alternative treatments to cope with problems that hearing aids cannot target, such as central age-related brain changes affecting speech processing in older adults.

1.2. Aims of the thesis

We formulated a variety of aims for this thesis in order to address the questions outlined above.

Aim I: Developing a test battery to assess central hearing loss in older adults. The experimental setup of Study I should involve psychoacoustic tasks to assess peripheral hearing as well as central and cognitive hearing. Furthermore, these hearing tests should assess the encoding of parameters relevant to the processing of a speech signal. Spoken language can be described as acoustic energy containing a variety of frequencies (spectral characteristics) developing and changing over time (temporal

characteristics). Thus, our hearing tests should assess the processing of temporal and spectral acoustic parameters. In addition, these hearing tests should contain a task which assesses the extent of the relation between cognitive functioning and speech understanding. It is important that all tests be adaptive, controlled for false positives, comprise a reliable number of trials, and be corrected for the individual peripheral hearing threshold.

Aim II: Describing neural correlates of central hearing loss. A second goal is to analyze the structural and functional neural fingerprints of central hearing loss by using multimodal neuroimaging data. The cortical regions of interest and the parameters representing the electrophysiological characteristics of speech processing should be selected based on current models of speech processing and not only investigate “where” in the brain the differences are, but also “how” the functioning differs with age. The structural and functional characteristics of auditory and higher language-relevant circuits in older adults without peripheral hearing loss should be compared to younger controls to obtain age-related changes. Furthermore, the neurophysiological age-related differences should be related to the performance in hearing tests developed for Aim I to assess relationships between age-related cortical structure and functioning, and central hearing loss.

Aim III: Designing a longitudinal study using central and cognitive hearing as outcome variables. In cross-sectional studies as applied in Aims I and II, development within the younger and older group cannot be assessed. For the future planning of interventions, knowledge about how adaptable the brain is to new situations (e.g., adapting to a new hearing aid after experiencing hearing loss) is indispensable. Thus, the goal of Aim III is to establish a longitudinal design using neural correlates for central and cognitive hearing as outcome variables. Importantly, the stimulus material should again comprise speech material and not be limited to simple sine wave tones. The paradigm should first be established by using a young control sample, which will allow for the formulation of precise hypotheses about the expected longitudinal modulations, and for the validation of the design and stimulus material.

Aim IV: Describing how hearing aids and hearing impairment in older adults affect central and cognitive hearing and their underlying neural functioning. Older hearing aid users with moderate age-related hearing loss should be compared to older adults without hearing loss regarding the neural processes reflecting central and cognitive hearing. Again, the stimulus material should consist of speech material and be based on the findings of Aim III. Furthermore, the effect of different hearing aid algorithms on central and cognitive hearing should also be assessed with the goal of objectively assessing the benefits of different algorithms.

Aim V: Describing how hearing aid use and moderate hearing impairment in older adults affect behavioral and neural plasticity during longitudinal auditory learning. Based on Aim III, the longitudinal design should be applied to the different samples of older adults established for Aim IV. This should not only allow for the investigation of cross-sectional differences between the groups (as in Aim IV), but also for the assessment of auditory learning as a function of age, hearing loss, and hearing aid algorithm.

Aim VI: Assessing how long the brain needs to acclimatize to a new hearing aid algorithm. One particular goal should also be to assess how long an older brain needs to adapt to a new hearing aid algorithm. From behavioral studies with children, we know that it takes time for a hearing aid (algorithm) to make an impact on speech processing and that individuals need to accumulate acoustic experience in order to benefit from a new hearing aid algorithm (Alexander, 2016; Wolfe et al., 2011, 2015). Therefore, we should also analyze how much time is required by the brain until a neural difference as a function of different hearing aid algorithms can be registered there.

In order to outline the motivation behind the aims and to relate them to the current literature, the following parts of the General Introduction in Chapter 1 contain background information for the three empirical studies described in Chapter 2. First, there will be a short summary of the current neurobiological models of central hearing and of auditory speech processing specifically, as evidenced from young, normal hearing individuals. Second, the predictions of these models will be linked to current evidence of speech processing difficulties, or central hearing loss, in older adults. Third, the

reasoning behind the choice of neuroscientific methods used to study central hearing in this PhD thesis will be described. Finally, in Chapter 3, all empirical findings of the experimental work will be integrated and discussed concerning their relevance and future directions of this research.

1.3. Central hearing – towards neurobiological models of speech processing

Almost 150 years ago, a French neurosurgeon and neuroanatomist named Paul Broca was consulted about two patients who were not able to produce speech. One of these patients was able to say only “tan tan” (Amunts and Zilles, 2006; Dronkers et al., 2007). Broca performed an autopsy on the patients’ brains after their deaths and described the lesions that he found on the surface of the left temporal lobe. Based on this observation, he formulated a first speech model of the brain, describing two speech centers in the left hemisphere. The anterior Broca Area was described as supporting speech production, while the posterior Wernicke Area was described as supporting speech perception (Amunts and Zilles, 2006; Dronkers et al., 2007).

This model, however, did not account for the complexity of speech processing. Research since then has surpassed this simplistic model of language by discovering and constantly improving modern neuroimaging methods such as magnet resonance tomography (MRI) and electroencephalography (EEG). Several modern theories provide far more detailed descriptions of the functional and anatomical correlates of speech processing in large networks in the left and right hemispheres (Friederici, 2012a; Hickok, 2009; Vigneau et al., 2006, 2011). However, it has also been noted that there might be an incommensurability problem when simply mapping linguistic units of language onto the brain (Poeppel, 2012). To overcome this problem, an emphasis should be put on the “how” and not just the “where” in the brain processes occur. In relation to this change of orientation, the *Asymmetric Sampling in Time* (AST) hypothesis by Poeppel (Doelling et al., 2014; Giraud and Poeppel, 2012a; Poeppel, 2001, 2003a, 2014) formulates the neural mechanisms of elemental acoustic speech processing in young and normal hearing adults: It is based on a definition of language which emphasizes the acoustic parameters in a speech signal rather than artificial linguistic units (Poeppel,

2012). To define the relevant acoustic parameters of a speech signal, it has to be described on a physical level. That is, the speech signal contains spectral power which unfolds over time on different, either rapid or slow, time scales, or so-called temporal cues. The key assumption of the AST hypothesis predicts that the processing of these temporal cues is differently preferred by the left and right auditory areas, these areas constituting of the superior temporal region with the planum temporale (PT), the planum polare (PP), the transverse temporal gyrus and the superior temporal sulcus (STS). It is assumed in the hypothesis that the left auditory areas preferentially extract rapidly changing acoustic cues and, therefore, information over short temporal integration windows (about 40 Hz, which corresponds to the gamma band in the human EEG). Alternatively, the right auditory cortex is assumed to preferentially process slowly changing cues, occurring over long integration windows (about 4 Hz, which corresponds to the theta band in the human EEG). More recent developments to the AST hypothesis describe the “how” of elementary speech processing even further: It is assumed that the incoming, slowly changing cues, such as prosody or intonation, are locked onto by the endogenous slow theta oscillations, while rapidly changing cues, such as phonetical information, are entrained by endogenous gamma oscillations (Doelling et al., 2014; Luo and Poeppel, 2007; Peelle et al., 2013; Zion Golumbic et al., 2012; Zion Golumbic et al., 2013). Thus, these two speech integration rates (based on oscillatory neural mechanisms) seem to parse and transfer the incoming sound to higher, language-relevant regions, in which meaning is then created out of these acoustic signals.

It is furthermore interesting to note that the functional asymmetries of the AST hypothesis have also been shown to be imprinted in spontaneous endogenous oscillations. These correlate with fluctuations around 3-6 Hz EEG rhythms in the right auditory areas and with fluctuations around 28-40 Hz EEG rhythms in the left auditory regions, a finding which is in agreement with the AST hypothesis (Giraud et al., 2007). In addition, the data from a study done by Morillon et al. (Morillon et al., 2010) shows that delta-theta and gamma asymmetric presence is confined to the language system and is absent from the motor and visual regions, an occurrence which suggests that these lateralized rhythms play a specific role in speech processing. Further, the authors of this paper describe the possibility of a micro-anatomical basis for these results, and state that the left auditory areas especially contain a great number of large pyramidal cells (Hutsler and Galuske, 2003), which typically show fast rhythmic bursting in the gamma

range (Gray and McCormick, 1996; Traub et al., 2003), while the right auditory areas show a greater proportion of smaller pyramidal cells. This is in line with the well-known, leftward morphological asymmetries in the planum temporale (PT) and Heschl's gyrus (HG) (Dorsaint-Pierre et al., 2006). Zatorre and Belin (Robert J Zatorre and Belin, 2001) showed that the two auditory areas in both hemispheres process temporal information (preferred in the left hemisphere) and spectral information (preferred in the right hemisphere) with a different resolution. They assumed that this functional asymmetry may be related to the anatomical hemispheric asymmetries in myelination and spacing of cortical columns, as it had previously been shown that there is greater myelination in the left auditory areas (Penhune et al., 1996), which can be associated with a greater sensitivity to rapid acoustic changes. Also, the more widely spaced cortical columns in the left auditory areas have been associated with integration over larger, tonotopically organized areas, thus leading to a poorer spectral resolution (Seldon, 1981).

Despite these discoveries, the relationship between the structural asymmetry of auditory areas and the functional asymmetry of language functions is not yet fully understood. To date, the functional part of this relationship has mainly been investigated by means of PET or fMRI. Unfortunately, these approaches are based on indirect measures of the brain's activity using the BOLD signal and biological tracers, respectively. The combination of neuroanatomical features with the direct measurement of brain activity by means of EEG has so far been neglected. Additionally, the lifespan stability of these structural and functional mechanisms is also not yet understood, despite existing evidence in favor of the AST hypothesis in young adults (Geiser et al., 2008; Hurschler et al., 2013, 2015, Liem et al., 2012a, 2014, Meyer et al., 2002, 2004; Zaehle et al., 2004). Thus, this thesis is one of the first to combine recent, parameter-based theories of speech processing, and to apply this combination in a research context on the speech processing of older adults with or without hearing loss, and with or without hearing aid treatment. But what do we know about speech processing in the aging brain so far?

1.4. The aging brain and speech processing

A series of studies has shown structural changes as measured by cortical thickness or cortical volume across the lifespan in subcortical and cortical areas. For example, the brain atrophies more and more with age, and this decline also applies to the brain regions relevant for speech processing (Raz et al., 2005; Resnick et al., 2003; David H. Salat et al., 2004; Sheppard et al., 2011; Patrick C M Wong et al., 2010). To illustrate this point, in a study by Sheppard et al. (2011), a significant positive correlation between cortical thickness and global network efficiency in the brain regions relevant for speech processing in noisy environments, such as the lateral temporal cortex, was found across both younger and older participants. Furthermore, another study found positive correlations between the ability to process speech in noisy environments and the direct cortical thickness of these respective areas (Patrick C M Wong et al., 2010). A pertinent question to ask at this point may be what exactly would having a thicker or a thinner cortex entail? The radial unit hypothesis by Rakic (Rakic, 2009) postulates that cortical thickness results from the number of neurons within each vertical column of cells in a specific brain region. Another important anatomical parameter is cortical surface area, which is primarily associated with the number of columns in a specific brain region (Rakic, 2009). Cortical surface area and cortical thickness are two independent neuroanatomical features. As the brain develops, these two features are influenced differently by certain factors (Frye et al., 2010). Specifically, cortical surface area increases during cortical folding, whereas cortical thickness is influenced by training, experience, disease, and plasticity across the lifespan (Meyer et al., 2013; Rakic, 1988). Thus, we assume that age-related cortical thinning, and the associated loss of synapses in auditory and other areas relevant for speech processing, may relate to the emergence of central hearing loss. One goal of this PhD thesis, therefore, was to investigate the relation between an age-related decline in cortical thickness and central hearing loss. Furthermore, we expected such structural differences to also be related to differences in neurofunctional organization. Previous studies combining anatomical and electrophysiological functional measures, such as theta and gamma oscillations, are scarce. Some attempts have been made to investigate

neurofunctional age-related changes in relation to speech processing difficulties in older adults, but most of these studies have been behavioral in nature.

One finding from this previous behavioral research is that older adults who suffer from presbycusis demonstrate a reduced ability to discriminate at the phonetic level, such as in the distinction between /da/ and /ga/ (Bellis et al., 2000; Giroud et al., in preparation). In addition, older adults are worse at discriminating between two syllables with very small stimulus onset asynchrony than younger or middle aged adults are (Fogerty et al., 2012a, 2012b). Another study investigated the effect of hearing loss on the perception of accented speech (Gordon-Salant et al., 2013). The authors of this study found that alterations in phonetic cues due to accent play a prominent role in intelligibility. It was shown that older adults with hearing loss performed worse than both older adults with normal hearing and younger adults in their attempts to comprehend accented speech. Discriminating between slightly different phonemes in an accented sentence is therefore an exceptionally difficult communication problem for older listeners.

A promising approach to the study of the neural substrates of such behavioral differences in speech processing in older compared to younger adults, is to assess auditory brainstem functioning during the processing of syllables such as /da/. For instance, it has been shown that, in this very early stage of processing, the electrophysiological signal as a reaction to vowel stimuli is delayed and blurred in older adults compared to younger adults. More specifically, the phase-locking between the frequency characteristics of the stimuli and the frequency details of the neurophysiological brainstem response are less correlated in older compared to younger adults (Anderson et al., 2012, 2013a, 2014; Parbery-Clark et al., 2012). Currently, we assume that these functional age-related differences may lead to the occurrence of problems with the processing of rapidly changing cues in older adults. But how is the processing of slowly changing cues affected?

It is worth noting that the declining effect of age is not apparent in the processing of slowly changing cues of speech. In fact, recent data from event-related potentials, a method used to study auditory perception with EEG, demonstrated clear online prosody effects (CPS and P600), which suggests that during the initial stages of processing,

younger and older adults' treatment of prosodic phrasing information does not differ substantially (Steinhauer et al., 2010). At a later stage, in which prosodically-driven, garden-path effects are integrated or (re)analyzed, some differences between younger and older adults do occur. It seems that older adults benefit from their familiarity with the fit between the meaning of lexical and syntactic structures with their prosody, which leads to a stronger P600 effect.

In sum, by combining the predictions of recent theories of the neurobiology of language for young adults with the behavioral literature on speech processing in older adults, we hypothesized that older adults would mainly have difficulties in the processing of rapidly changing cues, but not slowly changing cues, of speech. Thus, to study central hearing loss, we implemented behavioral tasks such as syllable discrimination, frequency discrimination, or gap detection tasks, to assess the processing of rapidly changing cues. Furthermore, the neurobiological aging indicates a possible link between anatomical age-related changes and difficulties in speech processing in noise in older adults, and therefore possibly also to central hearing loss. Consequently, structural MRI was assessed in both younger and older adults, and the relevant anatomical parameters were then related to the central hearing performance. Moreover, studies with young adults have shown that anatomical fingerprints may be related to the characteristics of neurofunctional organization relevant for speech processing, as also predicted by the AST hypothesis. Therefore, age-related structural changes were expected to be related to modulations in the neurofunctional organization in older adults, as well as in the studied electrophysiological oscillatory patterns and other EEG parameters relevant for speech processing in younger and older adults. Thus, this thesis represents a unique combination of interdisciplinary knowledge tailored to the goal of studying central hearing loss. In fact, the theoretical models of the neurobiology of language were connected with the aging literature and behavioral studies of speech perception in older adults. Moreover, phonetic knowledge was used to create the stimulus material for the experimental work, and clinical audiological research was referenced to study central speech processing in both hearing impaired and hearing aid users. This was particularly fruitful because the long term goal was (and continues to be) to apply the obtained knowledge in intervention studies. In line with this goal, longitudinal changes in central hearing were assessed as a function of hearing impairment and hearing aid treatment across three months. Methodologically, a variety

of neuroimaging methods was applied, such as structural MRI and EEG, to describe neural fingerprints of speech processing problems or central hearing loss in older adults. A more detailed description of the various neuroimaging methods used in this PhD thesis is in the following.

1.5. Neuroimaging methods

The experimental work for this PhD thesis was based on the application of multichannel electroencephalogram (EEG) technology (128 channel, Biosemi system and 256 channel Geodesic system). EEG is a non-invasive neuroimaging method used to measure electrical brain activity without adverse side effects. The procedure involves recording voltage fluctuations from both cortical and subcortical regions with electrodes connected to the scalp. EEG recordings provide a close to real-time neural signature of sensory and cognitive processing with a sampling rate of 500 Hz, meaning a temporal resolution of 2ms. This temporal resolution makes EEG technology superior to the widely-used functional magnetic resonance imaging (fMRI), and positron emission tomography (PET), both of which have a good spatial resolution but a much poorer temporal resolution (time range in seconds) than EEG. If the goal is to investigate temporal aspects of language processing that unfold in a time range of milliseconds, EEG is an appropriate technique. In the recent past the EEG technique has been significantly improved insofar as innovative spatio-temporal analysis techniques have been established that allow for the comprehensive investigation of cognitive functions (including speech, among others) by combining the analyses of various aspects of the EEG signal, namely source estimation, power spectra, oscillations, microstates and event-related brain potentials. This approach is called electrical neuroimaging (Michel et al., 2009b). The innovative character of the “Electrical Neuroimaging” approach almost guarantees novel insights into the complex matter of the language-brain relationship, and brings with it several important advantages (e.g., the analysis is reference-free, combines spatial and temporal information, and is devoid of any a priori assumptions of latency bands and regions of interest).

MRI scans were acquired using a 3.0 T Philips Intera whole-body scanner (Philips Medical Systems, Best, The Netherlands), which is equipped with a transmit-receive

body coil and a commercial 8-element sensitivity-encoding (SENSE) head coil array. A volumetric 3-dimensional (3D) T1-weighted gradient-echo sequence (turbo field echo) scan with a spatial resolution of $1 \times 1 \times 1$ mm (matrix 256×256 pixels, 160 slices) was conducted. Further imaging parameters were field of view = 240×240 mm, echo time = 2.3 ms, repetition time = 20 ms, and flip angle (α) = 8° . The preprocessing, the reconstruction of cortical surface segmentation was performed with the FreeSurfer image analysis suite (Dale et al., 1999a; B. Fischl et al., 1999a, 1999b, 2004; Fischl, 2012).

2. Empirical Part

2.1. Study I: Neuroanatomical and Resting State EEG Power Correlates of Central Hearing Loss in Older Adults

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Abstract

To gain more insight into central hearing loss, we investigated the relationship between cortical thickness and surface area, speech-relevant resting state EEG power, and above-threshold auditory measures in older adults and younger controls.

Twenty-three older adults and thirteen younger controls were tested with an adaptive auditory test battery to measure not only traditional pure-tone thresholds, but also above individual thresholds of temporal and spectral processing. The participants' speech recognition in noise (SiN) was evaluated, and a T1-weighted MRI image obtained for each participant. We then determined the cortical thickness (CT) and mean cortical surface area (CSA) of auditory and higher speech-relevant regions of interest (ROIs) with FreeSurfer. Further, we obtained resting state EEG from all participants as well as data on the intrinsic theta and gamma power lateralization, the latter in accordance with predictions of the Asymmetric Sampling in Time hypothesis regarding speech processing (Poeppel, 2003a). Methodological steps involved the calculation of age-related differences in behavior, anatomy and EEG power lateralization, followed by multiple regressions with anatomical ROIs as predictors for auditory performance. We then determined anatomical regressors for theta and gamma lateralization, and further constructed all regressions to investigate age as a moderator variable.

Behavioral results indicated that older adults performed worse in temporal and spectral auditory tasks, and in SiN, despite having normal peripheral hearing as signaled by the audiogram. These behavioral age-related distinctions were accompanied by lower CT in all ROIs, while CSA was not different between the two age groups. Age modulated the regressions specifically in right auditory areas, where a thicker cortex was associated with better auditory performance in older adults. Moreover, a thicker right supratemporal sulcus predicted more rightward theta lateralization, indicating the functional relevance of the right auditory areas in older adults.

The question how age-related cortical thinning and intrinsic EEG architecture relates to central hearing loss has so far not been addressed. Here, we provide the first neuroanatomical and neurofunctional evidence that cortical thinning and lateralization of speech-relevant frequency band power relates to the extent of age-related central hearing loss in older adults. The results are discussed within the current frameworks of speech processing and aging.

1. Introduction

The high prevalence of age-related hearing loss (presbycusis) (Brant and Fozard, 1990; Cruickshanks et al., 1998; Roth et al., 2011; Wiley et al., 2008) raises concerns that the number of individuals suffering from presbycusis and its serious consequences will continue to increase in aging Western societies (Lee et al., 2005; Wiley et al., 2008). To illustrate, approximately 55% of men and 45% of women in Europe at the age of 80 years currently experience a hearing loss of 30 dB or more (Roth et al., 2011). Moreover, many older adults remain untreated (Chien and Lin, 2012; Popelka et al., 1998) or do not wear the hearing aids that they have due to limited satisfaction (Bertoli et al., 2009). The high numbers of individuals without treatment of presbycusis is no less severe in the United States, where approximately 23 million older adults have untreated hearing loss (Chien and Lin, 2012).

Traditionally, hearing loss has been understood as peripheral hearing loss (Humes et al., 2012) and is normally measured by pure-tone audiometry (Pickles, 2012). Thus, hearing aids mainly focus on the treatment of peripheral hearing loss by amplifying sounds in order to improve audibility. However, recent research has shown that the causes of presbycusis are more complex and do not only involve peripheral hearing deficits (Humes et al., 2012; Wingfield and Peelle, 2015). Rather, it seems that presbycusis emerges out of an interaction of peripheral and central hearing loss. However, central hearing loss has so far been only vaguely described as an unspecific, age-related atrophy of the subcortical and cortical auditory circuitry, interacting with cognitive decline in aging adults (Huang and Tang, 2010b; Humes et al., 2012). In particular, many older adults have reported having speech processing problems, even when their peripheral hearing was normal or when audibility was restored (Füllgrabe, 2013; Füllgrabe et al., 2015; Hopkins and Moore, 2011; Moore et al., 2014; Pichora-Fuller and Souza, 2003). Despite this normal hearing or restoration, they continued to perform worse than younger adults in perceptual tasks, for example, involving temporal processing (Füllgrabe, 2013; Füllgrabe et al., 2015; Hopkins and Moore, 2011). The lower performance of older compared to younger adults in such perceptual tasks underlines the hypothesis that not only peripheral decline but also central decline may impact auditory perception in older adults. It is therefore of the utmost importance to

investigate not only audibility thresholds, but also supra-threshold auditory measures to better comprehend central hearing loss and its effects on speech processing. Thus, in the current work we used supra-threshold auditory tasks to measure frequency selectivity (FS) and temporal compression (TC). Moreover, we also collected data involving cognition on speech intelligibility. Specifically, a sentence intelligibility test was presented in background noise (SiN). Thus, the unique combination of tasks selected for this work allowed us to study the interaction between peripheral, central and cognitive hearing.

Furthermore, because there is only little knowledge about the occurrence of central hearing loss in older adults and because an overall treatment for the intertwined and multifactorial causes of presbycusis is currently unavailable (Huang and Tang, 2010b), it is crucial to study its underlying neuroplastic aspects. So far, previous studies that have attempted to describe the anatomical fingerprints of central hearing loss have used voxel-based morphometry (VBM) to detect morphological characteristics in older adults, with and without peripheral hearing loss (Eckert et al., 2012; Husain et al., 2011; Lin et al., 2014; Peelle et al., 2011). Notably, several studies showed lower cortical gray matter volume (CV) in the bilateral auditory areas in older adults with mild to moderate peripheral hearing loss when compared to normal hearing older adults (Eckert et al., 2012; Husain et al., 2011; Peelle et al., 2011). Moreover, longitudinal data underpinned the idea that peripheral hearing loss led to a decline in gray matter in auditory cortical areas, and showed that peripheral hearing loss predicted a stronger decline of CV in these regions, especially in the right hemisphere (Lin et al., 2014). Here, we define auditory areas as including the bilateral posterior part of the auditory-related cortex planum temporale (PT), the anterior part planum polare (PP), the part Heschl's gyrus (HG) and sulcus (HG), the superior temporal gyrus (STG), and the superior temporal sulcus (STS). Significant negative relations between the audibility thresholds in high frequencies and CV in bilateral Heschl's gyri further supported the interpretation that peripheral hearing loss negatively affected the morphology of the auditory cortex, probably through auditory deprivation (Eckert et al., 2012). However, one study (Profant et al., 2014) could not find the relation between elevated audibility thresholds and lower CV in the auditory-related cortex, and thus the authors attributed lower CV and also lower cortical thickness (CT) in the HG and the PT to the higher age of the participants, and not to their presbycusis. Furthermore, the structural decline in

auditory areas caused by aging has been shown to be more profound than the consequences of peripheral hearing loss would seem to suggest (Profant et al., 2014). Following that notion, in the current study we included one younger and one older group of participants, both with normal peripheral hearing as measured by the audiogram. By comparing younger and older adults with normal peripheral hearing, we were able to study the anatomical signatures of central age-related hearing loss, independent of peripheral hearing.

To investigate the anatomical emergence of central age-related hearing loss we used surface-based morphometry (SBM). SBM gives us the opportunity to evaluate cortical surface area (CSA) and CT separately. CV as measured by VBM was estimated by taking the product of CSA and CT (Panizzon et al., 2009). Thus, SBM minimizes the risk of ignoring differential relations between CT or CSA and behavior, as would be the case if CSA and CT were to relate to behavior in opposite directions. The advantage of an independent analysis of CT and CSA is further supported by a recent paper, which showed that the lateralization of several auditory areas varied as a function of CV, CT, and CSA (Meyer et al., 2014). CT and CSA have also been described as having no genetic relationship and as assessing different aspects of cortical structure (Rakic, 1988, 1995, 2007). Furthermore, it has been demonstrated that CT reflects dynamic modulations of training or experience across the lifespan (Bermudez et al., 2009; Engvig et al., 2010). In other words, age-related changes of the cerebral cortex are expected to be mainly driven by CT, not CSA (Meyer et al., 2014; Storsve et al., 2014a).

The missing link to neurofunctional age-related changes needs to be considered to get a comprehensive understanding of central age-related hearing loss. For instance, it has been shown that the combination of functional and structural data is particularly fruitful when investigating auditory processing (Liem et al., 2012b, 2013). Furthermore, from work with younger adults, there are several findings that link anatomical characteristics of left and right auditory areas to electrophysiological parameters (Liem et al., 2012b), and especially to intrinsic and evoked or induced oscillatory processes (Hutsler and Galuske, 2003; Penhune et al., 1996). First, left auditory areas are presumed to have more large pyramidal cells, which can produce fast gamma bursts, than right auditory areas (Hutsler and Galuske, 2003). Second, it has been shown that left auditory areas are more myelinated than the right, which suggests sensitivity for

rapid acoustic information (Penhune et al., 1996). In line with the Asymmetric Sampling in Time (AST) theory (Poeppel, 2003a), left and right auditory cortices preferentially sample sound at different rates; whereas the left auditory areas prefer rapidly changing acoustic information at approximately 40 Hz (gamma band), the right auditory areas preferentially process slower acoustic cues at approximately 4 Hz (theta band). Any incoming signal is then entrained at these two different rates into “chunks” of smaller (around 25 ms) and larger (around 250 ms) units. These two sampling rates are relevant to language because the faster sampling rate detects brief (sub)segmental cues of the speech signal, such as formant transitions or voice onset times, while the slower sampling rate picks up suprasegmental cues of the speech signal, such as prosody or intonation contour. The AST hypotheses has been confirmed by a number of studies using M/EEG in the last decade (Abrams et al., 2008; Doelling et al., 2014; Giraud and Poeppel, 2012a; Gross et al., 2013; Luo and Poeppel, 2007, 2012; Peelle and Davis, 2012; Pena et al., 2012; Rufener et al., 2016). Interestingly, it has also been shown that the functional oscillatory lateralization of the auditory areas as proposed by the AST framework is intrinsically imprinted in the auditory areas (Giraud and Poeppel, 2012a; Morillon et al., 2012) and not only evoked by incoming sound. Thus, in the current study we used resting state EEG to estimate the intrinsic theta and gamma power lateralization, in order to create a link between structure, function and behavior in older adults. It was our aim that the combination of resting state EEG, structural data, and supra-threshold hearing tests would then lead to a novel, integrated and comprehensive understanding of central hearing loss.

We hypothesized that older adults without peripheral hearing loss as tested in the audiogram would show lower performance in supra-threshold auditory and SiN tasks compared to younger adults (Füllgrabe, 2013; Füllgrabe et al., 2015; Hopkins and Moore, 2011; Moore et al., 2014; Pichora-Fuller and Souza, 2003), because it is assumed that central hearing loss is affected by age-related cortical atrophy, independent of peripheral hearing loss (Profant et al., 2014). Moreover, we expected this behavioral pattern to be generally reflected in thinner auditory and other speech-relevant cortices, as has previously been shown in the relation between higher pure-tone thresholds and lower CV (Eckert et al., 2012; Husain et al., 2011; Lin et al., 2014; Peelle et al., 2011; Patrick C. M. Wong et al., 2010). Furthermore, we also predicted that higher CT in auditory areas would be reflected in more right-lateralized theta power and more left-

lateralized gamma power as a flag for intact intrinsic auditory functional organization (Giraud et al., 2007; Morillon et al., 2012), because higher CT is related to more cells that can be firing synchronously, which may then lead to higher electrophysiological power being measured on the scalp.

2. Materials and Methods

2.1. Participants

Twenty-three healthy older adults (OA) (age range = 67-84 years, Mage = 72.39 years, 11 females) and thirteen younger controls (YA) (age range = 20-29 years, Mage = 24.15 years, 10 females) were recruited for this study. All older adults reached a score of at least 26 in the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). No past or current neurological or psychiatric diseases or ear/brain surgery were reported by the participants. Also, all participants denied having any language disorders, hearing disorders (such as tinnitus or sensorineural hearing loss) and/or dyslexia. Furthermore, all participants were native speakers of (Swiss-) German and did not practice more than six hours of music per week. Bilinguals were excluded from this study, meaning that none of the included participants learned a second language in preschool age. All participants were right-handed as assessed by the Annett Hand Preference Questionnaire (Annett, 1970a). Both age groups were matched for several cognitive factors, namely working memory and inhibition, as executive functioning ($t(34)=.56$, $p=.58$; $t(34)=-.20$, $p=.84$, respectively). Working memory was measured with the n-back task, while inhibition was assessed with the go/no-go task. Both factors were tested using the TAP test battery [Testbatterie zur Aufmerksamkeitsprüfung] (Bühner et al., 2006; Zimmermann and Fimm, 2002).

In addition, all participants passed the safety requirements for MRI scanning. The local ethics committee of the Canton Zurich approved the study, and written informed consent was obtained from all participants. Participants were paid for their participation.

2.2. Peripheral, central and cognitive hearing

We used four procedures to assess participants' peripheral, central and cognitive hearing. First, absolute pure tone thresholds were assessed. Then, two supra-threshold measures were obtained, one for frequency selectivity (FS) and one for temporal compression (TC) (Lecluyse et al., 2013; Lecluyse and Meddis, 2009). Last, a SiN sentence intelligibility task was conducted using the Oldenburg Sentence Test (OLSA) (Wagener et al., 1999a, 1999b, 1999c). All tests were performed by a licensed audiologist in a double-walled, sound-attenuated booth. The procedure and the stimuli have already been described in earlier studies (Kegel et al., in preparation; Lecluyse et al., 2013). The acoustic signals for the pure tone audiometry and both supra-threshold measures were coupled with circumaural headphones (Sennheiser HD 280-13 300 Ω), while a custom-written Matlab software controlled the stimulus presentation. Participants were seated in front of a touch screen (ELO AccuTouch, version 5.5.3.6.) on which they could register their answers.

2.2.1. Peripheral hearing: Absolute thresholds

Only normal hearing adults (age adequate) were included in this study. According to the hearing impairment grading scale of the World Health Organization (WHO), a pure-tone average (PTA) of 25 dB or less (for frequencies 500, 1000, 2000 and 4000 Hz) is graded as "no impairment", while a PTA between 26 and 40 dB is rated as a "slight impairment". In the present study, we chose to exclude participants with a greater PTA than 30 dB to ensure that all test items of the experiment will be audible for the participants and that the thresholds do not signal a hearing loss that would be diagnosed in the clinic. Correspondingly, participants with asymmetrical hearing loss (more than 15dB difference between left and right ear) were also excluded.

Absolute thresholds were assessed using a probe-detection paradigm with pure tones presented for 250 ms at 500, 1000, 2000, and 4000 Hz. The audiograms are depicted in Figure 1.

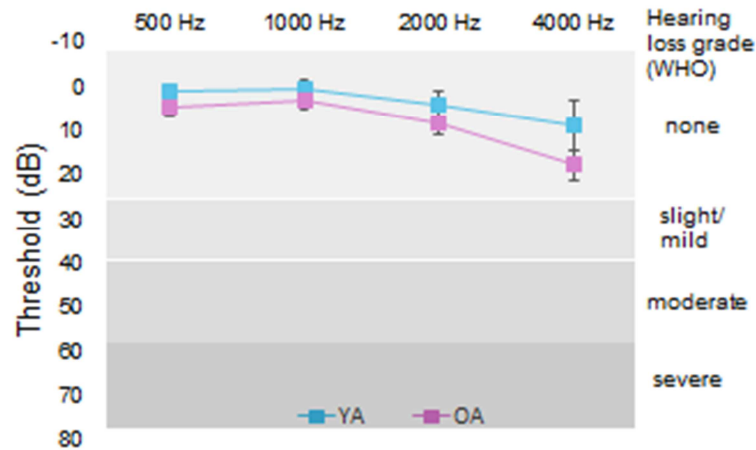


Figure 1 depicts the pure-tone audibility thresholds as measured with traditional audiometry, separately for the young (YA) and older (OA) adults for 0.5, 1, 2, and 4 kHz tones. On the right, the World Health Organization (WHO) classification of hearing loss burden is described.

2.2.2. Central hearing: Supra-threshold frequency selectivity (FS)

To obtain a measure for FS, a forward-masking paradigm was used. The paradigm consisted of a 108 ms masker followed by a 16 ms probe tone presented at ≥ 10 dB above the individual absolute threshold, with a 10 ms gap between the masker and the probe. The lowest level of the masking tone that was able to prevent the perception of the probe tone was identified. The level of the masker was varied adaptively between trials with a single-interval adaptive tracking procedure. In other words, the masker level either decreased or increased in 2 dB steps, dependant on the accuracy of the participants' answers. This adaptive procedure was applied to four probe frequencies (500, 1000, 2000, 4000 Hz), for which the masker frequencies varied in relation to the respective probe frequency (0.7:1, 0.9:1, 1:1, 1.1:1, 1.3:1). Participants were instructed to indicate whether they heard none, one or two tones. They were able to repeat each trial as many times as they wanted. To make the task as user-friendly as possible, the start of each trial was indicated by a cue tone, which was presented 500 ms before the masker. As a parameter for statistical analysis, the depth between masker levels at the highest and the lowest frequency obtained during testing can be calculated for each probe frequency, and then averaged across the four probe frequencies. This calculation has been shown to be a valid parameter for the description of FS in normal hearing and hearing impaired adults (Lecluyse et al., 2013).

2.2.3. Central hearing: Supra-threshold temporal compression (TC)

The procedure to assess TC is similar to that used for assessing the FS. Again, a forward-masking task with a masker and a probe, presented at ≥ 10 dB above the individual absolute threshold was used, while an adaptive procedure was again applied to assess the lowest level of the masking tone, which prevented the perception of the probe. Here, the gap between the masker and the probe varied between 10, 30, 50, and 70 ms, while, as before, four gap and masker frequencies were used (500, 1000, 2000, and 4000 Hz). The steepness of the slope as a function of gaps for each frequency tested indicates the compression. Here, the slope is assessed for each frequency and then averaged to obtain a parameter that best describes TC differences between normal hearing and hearing impaired participants (Lecluyse et al., 2013).

The two tasks FS and TC are indirectly linked to speech processing, which is the reason why they were selected for this work. Both parameters, the FS and the TC, are related to speech processing in that they represent the two most important cues in any speech signal: A speech signal can be described as acoustic power varying in frequencies (FS) and changing across time (TC).

2.2.4. Cognitive hearing: Speech-in-noise sentence intelligibility

A signal-to-noise ratio (SNR) was measured with the OLSA Matrix Sentence SiN test (Wagener et al., 1999a, 1999b, 1999c). Speakers for sentences and background noise were positioned 0° azimuth and 1.5 meters away from the seated subject's head. The sound was presented using MACarena software. Sentences and noise were initially presented at 65 dB SPL, while sentence level was adaptively varied after each response in order to assess the SNR at which the participant was able to correctly repeat 50% of the words in a sentence. Participants were instructed to repeat as many words as possible after each sentence. The audiologist documented the participant's responses. The noise used in this study was generated by 30 random overlays of the whole test material, leading to a noise with low amplitude modulations and of the same spectrum as the test sentences. The sentences were low-context sentences, meaning that the guessing of the words from the context was excluded.

2.3. MR acquisition and T1-weighted image processing

Anatomical MR scans were obtained from a 3.0 T Philips Ingenia scanner (Philips Medical Systems, Best, The Netherlands) with a 12 channel head-coil. A high resolution T1-weighted anatomical 3D Turbo-Field-Echo (TFE) sequence was used with echo time (TE) = 3.79 ms, repetition time (TR) = 8.18 ms, field of view (FOV) = 240 x 160 x 240 mm, acquisition matrix = 256 x 256, 160 slices per volume, and isotropic voxel size = 0.94 x 0.94 x 1 mm, flip angle (α) = 90°. For four older participants, only one T1-weighted image was obtained, whereas for all other participants, two T1-weighted images were acquired.

Cortical surface reconstruction was performed with the FreeSurfer image analysis suite (version 5.1.0.). The software is documented online and freely available (<http://freesurfer.net/>). Surface-based morphometry (SBM) implemented in the FreeSurfer pipeline involves several preprocessing steps, which have already been described extensively in prior publications (Dale et al., 1999b; Dale and Sereno, 1993; Bruce Fischl et al., 1999a, 1999b, Fischl et al., 2001, 2002, Bruce Fischl et al., 2004a, 2004b; Fischl and Dale, 2000; Reuter et al., 2010; Ségonne et al., 2004). The two T1-weighted images were averaged (Reuter et al., 2010) to create a single image volume with high contrast-to-noise. The pipeline proceeds in a fully automated way, and generates individual cortical surface models with millimeter precision. Furthermore, all brains were manually checked for the segmentation precision, but no manual editing of the segmentation was conducted. However, one older adult was excluded because of failed surface reconstruction of the T1-weighted image. After preprocessing, FreeSurfer allows for the extraction of cortical thickness (CT) and cortical surface area (CSA) at each vertex of the surface. CT is defined as the minimal distance between gray-white matter border and the pial surface at each vertex of the tessellated surface (Fischl and Dale, 2000). CSA is specified as the mean area of the region at the respective vertex, while cortical volume (CV) is the arithmetic product of CT and CSA. In this paper, we used the mean of the pial surface area and the gray-white matter surface area as mean CSA in order to get a more comprehensive measure of the surface. CT has so far been validated by using manual segmentations (Cardinale et al., 2014; Kuperberg et al., 2003; D. H. Salat et al., 2004), and histological analysis (Rosas et al., 2002), and has been shown to be reliable in healthy older adults (Liem et al., 2015). The cortex was parcellated into

regions of interest (ROIs) by using the *aparc.a2009s* annotation (Destrieux et al., 2010), which has been used previously in similar studies (Meyer et al., 2014).

In total, eleven ROIs were selected bilaterally based on previous studies that showed the involvement of these regions in auditory perception and speech processing (see Figure 2). First, auditory regions were selected based on previous publications (Meyer et al., 2014; Wong et al., 2008). These ROIs included bilaterally the planum temporale (PT), the planum polare (PP), the superior temporal gyrus (STG), the superior temporal sulcus (STS), Heschl's gyrus (HG), and Heschl's sulcus (HS). Second, according to current neurobiological language frameworks (Friederici, 2012b; Hickok and Poeppel, 2007; Vigneau et al., 2011), we selected several higher-order language related ROIs that have been described as being relevant to speech processing, such as the pars triangularis (BA 45, PTRI), the pars opercularis (BA 44, POP), and the pars orbitalis (BA 47, POR). In addition, the precuneus (PCUN) has been shown to be activated during speech-in-noise (SiN) sentence processing, and has been shown to be an anatomical correlate of SiN tasks (Wong et al., 2009; Patrick C. M. Wong et al., 2010). The dorsolateral prefrontal cortex (dlPFC) was also included as a ROI because of its role in higher-order language processing (Gabrieli et al., 1998; Sheppard et al., 2011). The labelling of the dlPFC was created by merging the superior frontal gyrus, the rostral middle frontal gyrus, and the caudal middle frontal gyrus (Lundquist, 2009). The caudal part of the label was subsequently coronally cut at Talairach coordinate $y = 26$ (Rajkowska and Goldman-Rakic, 1995), while a crop along the superior part of the medial wall was created to separate the medial from the lateral part. In addition, we used two primary sensory non-auditory control regions, namely the bilateral visual cortex, here defined as the average of the occipital pole and the calcarine sulcus which overlap with V1, and the bilateral somatosensory cortex, here defined as the postcentral gyrus.

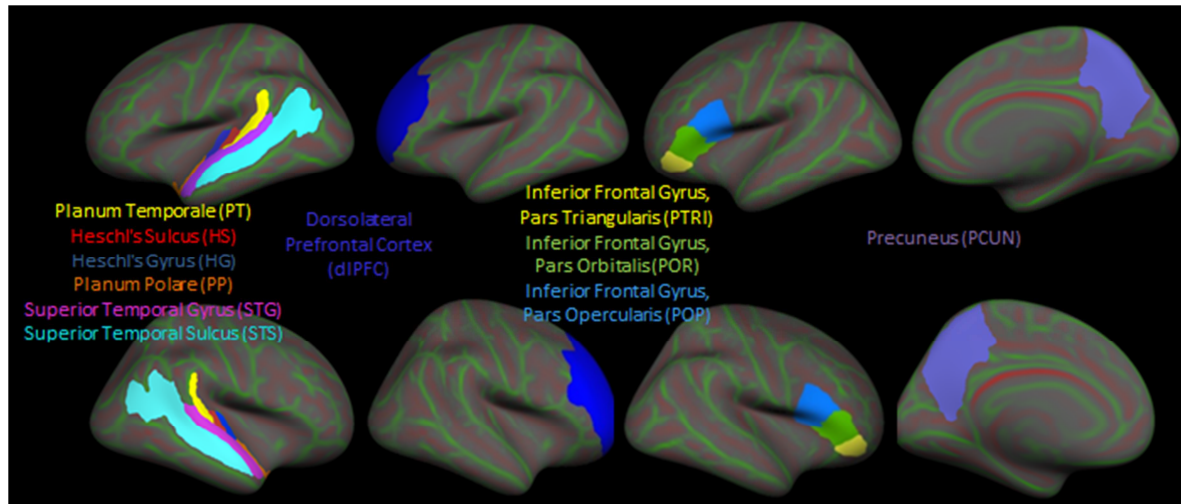


Figure 2 shows the eleven regions of interest (ROIs) chosen for this study. From these regions, cortical thickness (CT) and cortical surface area (CSA) for both hemispheres were extracted with FreeSurfer using the *aparc.a2009s* annotation (Destrieux et al., 2010).

2.4. EEG recording and preprocessing

EEG was continuously recorded by using a 128 electrode system (BioSemi AcitveTwo, Amsterdam NL) and was digitized at a sampling rate of 512 Hz. The data was online band-pass filtered between 0.1-100 Hz, while the impedances for all electrodes were kept below 30 k Ω . We recorded about two minutes of eyes open, followed by eyes closed resting state and analyzed about one minute (30 – 90 s after recording start) of the eyes-open resting state, during which participants were instructed to direct their eyes to a fixation cross, presented in the middle of a screen. Brain Vision Analyzer Software (Version 2.1.0, Brainproducts, Munich, Germany) was used for the preprocessing steps. First, the data was bandpass filtered between 0.1-80 Hz using a notch filter. We applied an independent component analysis (ICA) to remove eye movements and eye blinks (Jung et al., 2000), and then interpolated the noisy channels (Perrin et al., 1987). Movement artifacts and other artifacts were removed with a semi-automatic raw data inspection. Further, the data was re-referenced to the average reference. After the data was clean, it was segmented into 2000 ms segments. Power spectra were calculated for each trial and averaged for each participant in order to obtain resting-state activity. We extracted theta-band (3-7 Hz) and low gamma-band (30-45 Hz) power for two symmetrical regions of interest on the scalp, namely left auditory (pooled electrodes: 1-D10, 1-D21, 1-D22, 1-D23, 1-D24, 1-D25, 1-D26, 1-D29, 1-D30, 1-D31, 1-D32, 1-D5, 1-D6, 1-D7, 1-D8, 1-D9) and right auditory (pooled

electrodes: 1-B10, 1-B11, 1-B12, 1-B13, 1-B14, 1-B15, 1-B16, 1-B24, 1-B25, 1-B26, 1-B27, 1-B28, 1-B29, 1-C5, 1-C6, 1-C7), because we decided to focus on the lateralization of theta and gamma power as these frequency bands have both been shown to be most relevant for speech processing (Giraud et al., 2007; Morillon et al., 2010).

2.5. Statistical analyses

Several covariates were used for the regression analyses and correlations for all sorts of data gathered. First, when analyzing the younger participants, gender was included as a covariate because of its unequal distribution within the younger group. Second, the computations including CSA were corrected for intracranial volume (ICV) (O'Brien et al., 2011).

The first goal of the study was to examine group differences in CT and CSA for the 11 bilateral ROIs. Therefore, independent t-tests were performed and directly corrected for multiple comparisons by applying the Bonferroni correction (alpha error divided by the number of tests). This procedure lowered the alpha level from $\alpha = .05$ to $\alpha = .0023$ for the 22 ROIs compared between the two age groups (Patrick C. M. Wong et al., 2010). Furthermore, we evaluated for the presence of significant lateralizations in resting state theta and gamma power by calculating a lateralization index (LI), which is defined as the power of the left electrode pool minus the power of the right electrode pool. In other words, a positive LI indicates left lateralization, while a negative LI implies right lateralization. We then computed a t-test against zero to uncover any significant lateralizations for the younger and older adults and computed independent t-tests to explore age-related differences in lateralization of theta and gamma power. Subsequently, independent t-tests were performed to explore age-related differences in the behavioral auditory tests. In order to assess if auditory performance can be predicted by anatomical traits, such as the CT and CSA of the cortical ROIs, hierarchical stepwise multiple regressions were calculated. These included both age groups and their interactions to assess whether age moderates the relation between anatomy and hearing. The anatomical parameters were z-standardized and correlation coefficients among predictors were checked to not be higher than .8 (which was the case except for right-left precuneus thickness which was slightly above .8 with $r = .808$) to reduce multicollinearity. Further, to obtain relationships between auditory CT and

theta/gamma resting state lateralization, we conducted hierarchical stepwise multiple regressions with z-standardized CT values of auditory ROIs as independent variables and LI of gamma and theta as dependent variables in order to investigate within and between group effects.

Unless otherwise indicated, an alpha level of $\alpha = .05$ was accepted and effect sizes were indicated by partial eta-squares (η^2_p).

3. Results

3.1. Age-related differences in central and cognitive hearing

The profiles for FS are depicted in Figure 3A and for TC in Figure 3B. For FS, we found lower performance in the older compared to the younger adults, in the averaged depth value ($t(29)=4.27$, $p<.001$, two-tailed) and in the 4 kHz depth value ($t(28)=4.43$, $p<.001$, two-tailed) (see Figure 3C), even though the tests were conducted on a supra-threshold level. Furthermore, the older adults achieved lower supra-threshold temporal compression, as compared to the younger adults, in the 4 kHz slope ($t(31)=2.76$, $p=.01$, two-tailed). This finding was also reflected by a trend for the averaged slope ($t(31)=1.86$, $p=.07$, two-tailed) (see Figure 3C). In addition, older adults showed lower tolerance towards a low speech level when noise was presented simultaneously as evidenced by the higher SNR in the speech-in-noise test ($t(34)=-8.31$, $p<.001$, two-tailed) (see Figure 3D).

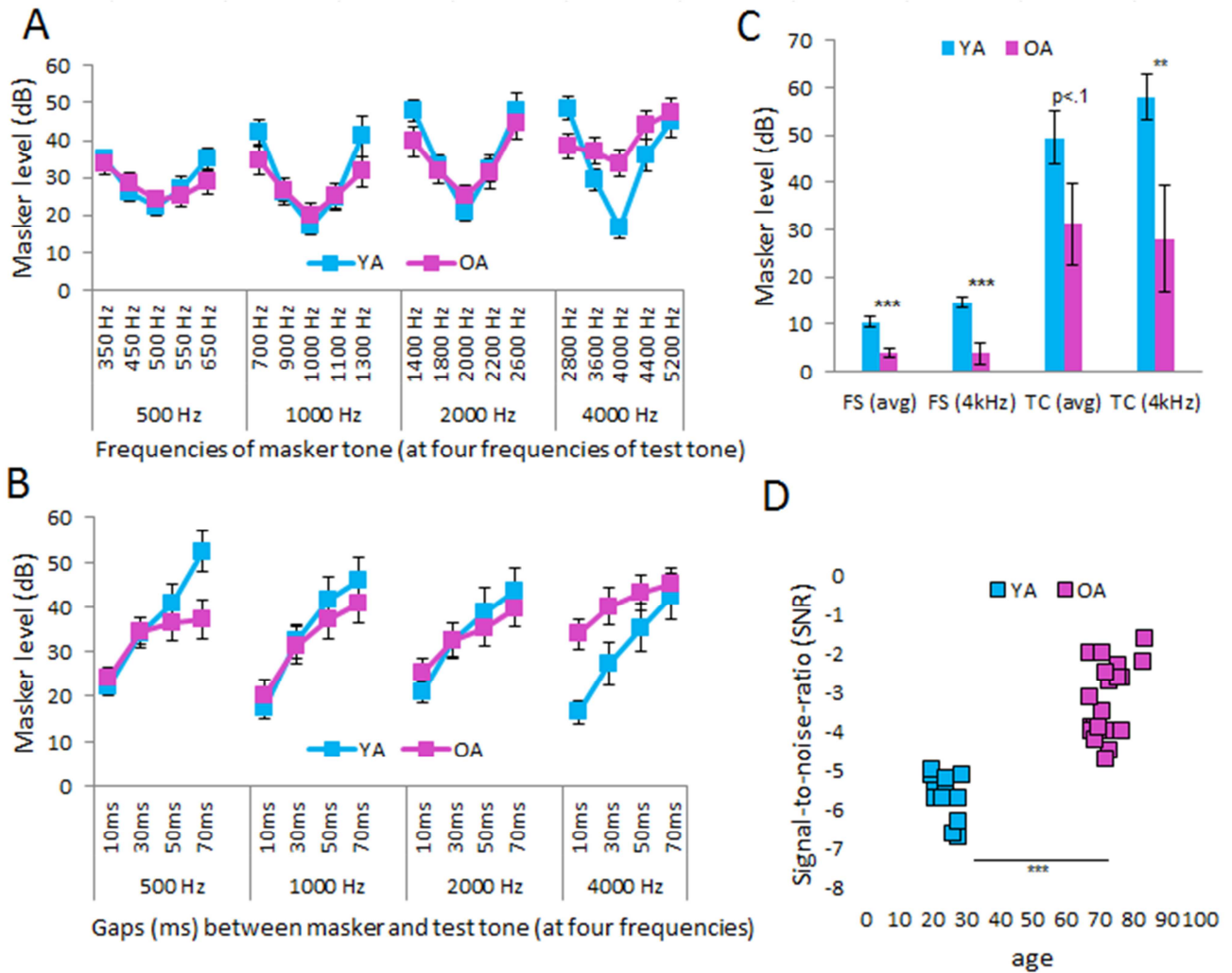


Figure 3(A) shows the behavioral profiles of the frequency selectivity (FS) task for younger (YA) and older (OA) separately. The adaptive procedure identified the lowest level of the masking tone being able to prevent perceiving the probe tone (y-axis). This approach was applied to four probe frequencies (500, 1000, 2000, 4000 Hz), for which the masker frequencies varied in relation to the respective probe frequency (0.7:1, 0.9:1, 1:1, 1.1:1, 1.3:1). Figure 4(B) depicts the behavioral profiles of the temporal compression (TS) task, separately for YA and OA. The lowest level of the masking tone, which prevented perceiving the probe, was assessed with an adaptive procedure (y-axis). Here, the gap between the masker and the probe varied between 10, 30, 50, and 70 ms, while four gaps were used at each of the four masker frequencies (500, 1000, 2000, and 4000 Hz). Figure 3(C) depicts the mean depth of each structure, first averaged for the four masker tones, and second for the 4 kHz masker tone, for YA and OA. Highly significant lower mean depth ($p < .001$) were obtained for OA compared to YA, an indicator for lower supra-threshold frequency compression in OA. Furthermore, the steepness of the slope as a function of gaps for each masker frequency in TC was averaged across all masker frequencies and also shown only for the slope at the masker frequency of 4 kHz. Moreover, Figure 4(D) shows the significant lower ($p < .001$) signal-to-noise-ratio (SNR) in the speech-in-noise (SiN) sentence recognition test, indicating lower tolerance of noise in OA compared to YA.

3.2. Age-related differences in cortical thickness and cortical surface area

Figure 4 shows the differences in CT and CSA of all ROIs in the left and right hemisphere between the two age groups.

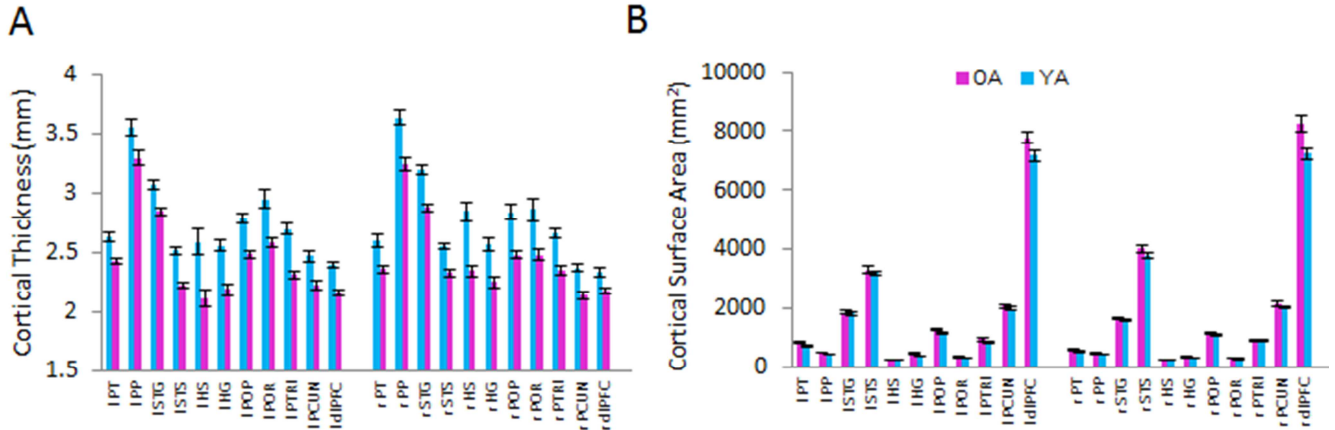


Figure 4(A) depicts cortical thickness (CT) in mm, extracted with FreeSurfer using the aparc.a2009s annotation (Destrieux et al., 2010), for all regions-of-interest (ROI) used in this study. Differences between younger (YA) and older adults (OA) are shown. All ROIs, except the left planum temporale (PT) have significantly lower CT in older, compared to younger adults with $p < .0023$ (Bonferroni corrected). See also Table 1 for mean CT, standard deviation of CT and t-values for statistical comparison of YA and OA. Figure 3(B) shows the mean cortical surface area (CSA) in mm², as calculated with the aparc.a2009s annotation in FreeSurfer (Destrieux et al., 2010). When lowering the p-value to $p < .0023$ to correct for multiple comparison (Bonferroni corrected), none of regions-of-interest (ROI) show significant differences between younger (YA) and older adults (OA).

We found strong age-related differences in CT in all ROIs, except in the left PP ($p = .011$, uncorr.). In other words, all older adults had lower CT than the younger adults in all brain areas investigated in this study (see Table 1). In the control regions, we also found lower CT in OA than in YA in the visual cortex ($p < .001$), but no age-related differences in CT of the somatosensory cortex ($p = .33$).

However, the mean CSA group comparisons (Bonferroni corrected) showed no differences between older and younger adults (see Table 2) in all regions, as well as in control regions (visual cortex $p = .23$, somatosensory cortex $p = .45$).

Table 1 shows the mean (M) and standard deviation (SD) of cortical thickness (CT) of all eleven bilateral ROIs used in this study, separately for YA and OA. Two-sampled t-test indicates differences between age groups, while p-value was lowered according to Bonferroni to correct for multiple comparisons.

	YA		OA		t	p
	M	SD	M	SD		
l PT	2.63	.15	2.43	.12	t(34)=4.42	<.001 ***
l PP	3.55	.24	3.29	.29	t(34)=2.68	.011
l STG	3.06	.16	2.85	.16	t(34)=3.91	<.001 ***
l STS	2.52	.12	2.23	.11	t(34)=7.38	<.001 ***
l HS	2.59	.39	2.12	.35	t(34)=3.72	.001 *
l HG	2.56	.19	2.19	.22	t(34)=5.06	<.001 ***
l POP	2.79	.12	2.48	.16	t(34)=5.94	<.001 ***
l POR	2.95	.26	2.58	.19	t(34)=4.78	<.001 ***
l PTRI	2.70	.16	2.31	.17	t(34)=6.68	<.001 ***
l PCUN	2.47	.18	2.22	.18	t(34)=3.98	<.001 ***
l dlPFC	2.40	.08	2.16	.10	t(34)=7.22	<.001 ***
r PT	2.60	.18	2.36	.16	t(34)=4.06	<.001 ***
r PP	3.63	.23	3.24	.30	t(34)=4.14	<.001 ***
r STG	3.19	.13	2.87	.17	t(34)=5.90	<.001 ***
r STS	2.55	.08	2.33	.14	t(34)=5.16	<.001 ***
r HS	2.84	.28	2.34	.25	t(34)=5.52	<.001 ***
r HG	2.57	.21	2.25	.24	t(34)=4.14	<.001 ***
r POP	2.84	.20	2.48	.14	t(34)=6.34	<.001 ***
r POR	2.86	.34	2.48	.24	t(34)=3.93	<.001 ***
r PTRI	2.66	.14	2.35	.17	t(34)=5.57	<.001 ***
r PCUN	2.37	.12	2.14	.18	t(34)=4.16	<.001 ***
r dlPFC	2.33	.14	2.18	.10	t(34)=3.88	<.001 ***

Note: $p<.05$ trend, $*p<.0023$, Bonferroni corrected, $***p<.001$

Table 2 describes the mean (M) and standard deviation (SD) of mean cortical surface area (CSA) for YA and OA of all eleven bilateral ROIs used in this study. Two-sampled t-test were computed to reveal group differences. To correct for multiple comparisons, the p-value was lowered according to Bonferroni correction.

	YA		OA		t	p
	M	SD	M	SD		
l PT	801.92	138.71	692.07	104.73	t(34)=2.69	.011
l PP	465.81	52.92	416.83	50.95	t(34)=2.73	.010
l STG	1852.73	167.02	1802.28	168.66	t(34)=.87	.393
l STS	3297.54	479.84	3185.61	427.26	t(34)=.72	.475
l HS	244.27	28.78	241.57	37.45	t(34)=.23	.823
l HG	438.38	92.08	371.85	54.75	t(34)=2.38	.029
l POP	1264.50	107.41	1110.46	153.73	t(34)=3.19	.003
l POR	318.46	40.68	295.20	31.77	t(34)=1.91	.065
l PTRI	924.85	170.58	840.52	122.82	t(34)=1.72	.095
l PCUN	2062.46	194.41	1960.26	290.02	t(34)=1.13	.266
l dlPFC	7777.69	693.73	7157.72	880.02	t(34)=2.81	.036
r PT	553.31	81.47	518.04	62.10	t(34)=1.46	.153
r PP	462.65	60.56	433.37	58.65	t(34)=1.42	.164
r STG	1628.00	158.71	1557.07	161.25	t(34)=1.28	.211
r STS	4009.81	415.10	3795.76	421.50	t(34)=1.47	.150
r HS	203.00	27.67	206.70	27.56	t(34)=-.39	.702
r HG	319.46	53.66	273.50	40.64	t(34)=2.90	.006
r POP	1148.23	161.24	1087.54	153.43	t(34)=1.12	.271
r POR	270.15	42.88	249.48	39.64	t(34)=1.46	.153
r PTRI	897.00	154.53	874.26	185.45	t(34)=.37	.711
r PCUN	2154.27	274.50	2006.65	207.61	t(34)=1.82	.077
r dlPFC	8240.81	1016.61	7230.54	950.92	t(34)=2.99	.005

$p<.05$ trend, $*p<.0023$, Bonferroni corrected, $***p<.001$

3.3. Age-related differences in lateralization of theta and gamma oscillations in resting state

The independent t-tests against zero for the LI parameters could not demonstrate significant lateralization in theta (LI theta: $M=.01$, $SD=.26$, $t(12)=.19$, $p=.85$, two-tailed), nor in gamma (LI gamma: $M=.04$, $SD=.12$, $t(12)=1.23$, $p=.24$, two-tailed) for the younger adults. However, the older adults showed a significant rightward asymmetry of theta power (LI theta: $M=-.08$, $SD=.16$, $t(21)=-2.44$, $p=.02$, two-tailed) (see Figure 6B), but no significant lateralization of gamma power (LI gamma: $M=-.04$, $SD=.20$, $t(21)=-.93$, $p=.36$, two-tailed). We found trends for age-related differences in lateralization of theta ($t(33)=1.37$, $p=0.09$, one-tailed) and gamma ($t(33)=1.32$, $p=0.10$, one-tailed) revealing a trend towards stronger right-lateralization of theta and gamma power in older compared to younger adults.

3.4. Associations between anatomy and hearing

3.4.1. Cortical thickness

All significant results of the multiple regressions using CT as predictors are shown in Figure 5A. Using FS as a dependent variable ($F(3,27)=11.27$, $p<.001$, $R^2_{corr}=.51$), we found that a thicker left dlPFC predicted better FS performance across all participants ($\beta=.47$, $p=.008$). Furthermore, we found a significant interaction with age group in the right PT, where a thicker cortex only predicted better FS performance in the OA ($\beta=.40$, $p=.015$).

For the analysis with TC as a dependent variable ($F(2,32)=3.61$, $p=.039$, $R^2_{corr}=.14$), we found a significant interaction with age group, which suggested that a thicker right HS only predicted better TC performance in OA ($\beta=.43$, $p=.014$).

For the regression analysis with the SNR of the SiN test as an outcome ($F(5,30)=23.23$, $p<.001$, $R^2_{corr}=.76$), the analysis revealed that a thicker left POR ($\beta=-.59$, $p<.001$) and a thicker left PTRI predicted lower SNR ($\beta=-.43$, $p=.001$) (more tolerance towards background noise). In addition, two interactions suggested that only in OA a

thicker right HS ($\beta=-.30, p=.007$) and a thinner right POR ($\beta=.33, p=.013$) predicted lower SNR.

For the control regions, we calculated similar regression analyses and found that FS ($F(2,28)=5.14, p=.013, R^2_{corr}=.22$), TC ($F(2,30)=3.40, p=.047, R^2_{corr}=.13$), and the SNR of the SiN ($F(2,33)=12.46, p<.001, R^2_{corr}=.40$) were predicted positively by the CT of the visual cortex, while no interactions with group were found. Thus, a thicker visual cortex related to better performance in FS ($\beta=.51, p=.004$), TC ($\beta=.41, p=.017$) and lower SNR in the SiN ($\beta=-.65, p<.001$). No significant regressions were found for the CT of the somatosensory cortex (FS: $F(1,29)=1.79, p=.675, R^2_{corr}=.02$, TC: $F(1,31)=.32, p=.577, R^2_{corr}=.02$, SNR of the SiN: $F(1,34)=43, p=.519, R^2_{corr}=.01$), which supports the interpretation that our results are specific to age-related plasticity in hearing.

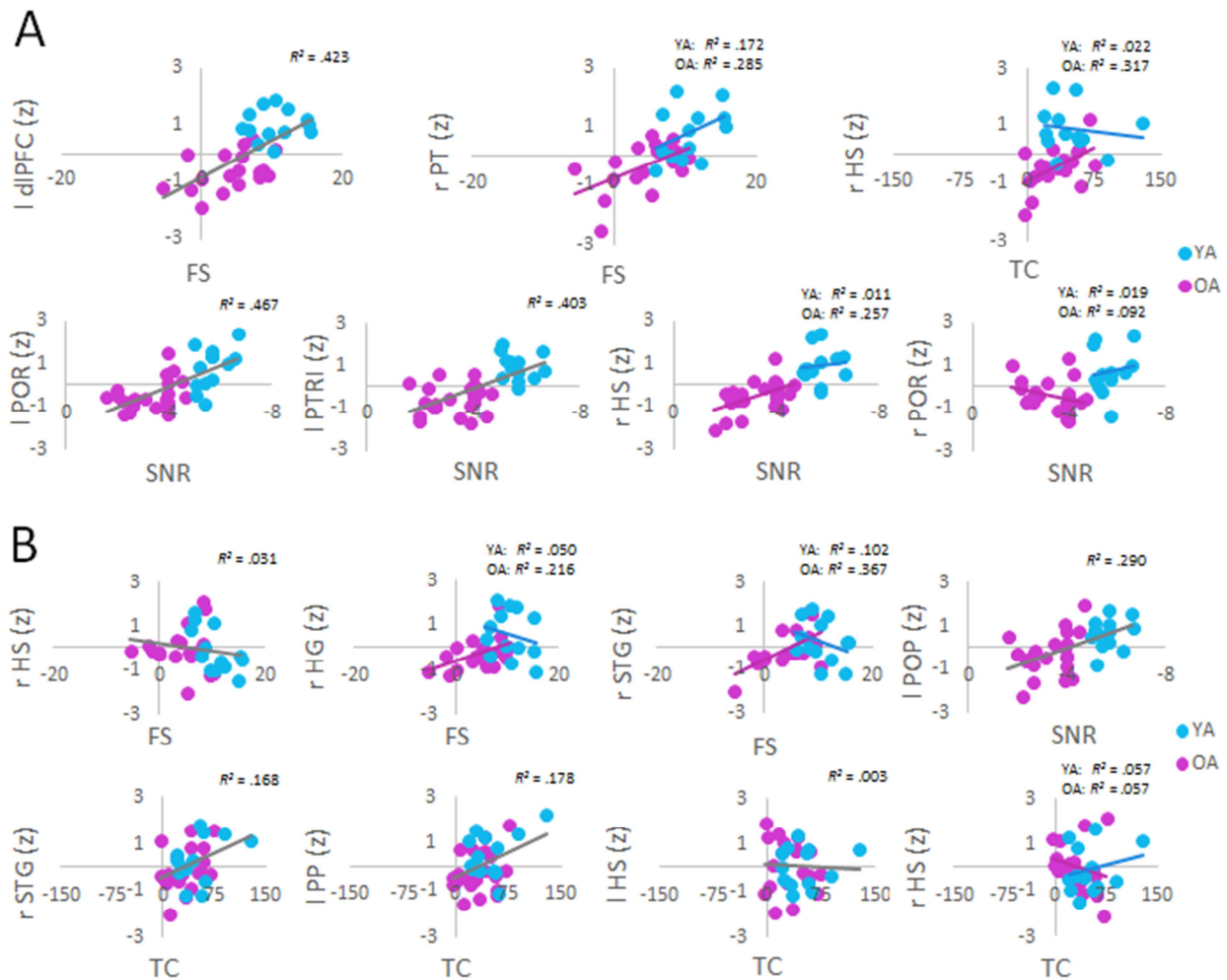


Figure 5(A) depicts the significant predictors and interactions with age of the multiple regression analyses with cortical thickness (CT) (z-standardized) of all eleven bilateral ROIs used in this study as predictors and the auditory tasks as outcome variables. Figure 5(B) shows the significant predictors of the multiple regression analyses with mean cortical surface area (CSA) (z-standardized) of all eleven bilateral ROIs used in this study as predictors and the auditory tasks as outcome variables.

3.4.2. Cortical surface area

The significant relations of the multiple regressions using CSA as predictors are depicted in Figure 5B. The multiple regression analysis with FS as a dependent variable ($F(5,25)=5.12$, $p=.002$, $R^2_{corr}=.41$) showed that a smaller mean CSA in the right HS predicted better FS performance ($\beta=-.61$, $p=.002$) across all participants. Two interactions with age group suggested that, only in OA, bigger mean CSA in right HG ($\beta=.54$, $p=.007$) and right STG ($\beta=.39$, $p=.039$) predicted better FS performance.

For the TC ($F(6,26)=4.73$, $p=.002$, $R^2_{corr}=.41$), the analysis revealed that bigger mean CSA in right STG ($\beta=.57$, $p=.003$) and left PP ($\beta=.49$, $p=.008$) and smaller mean CSA in left HS ($\beta=-.38$, $p=.022$) predicted better performance. Moreover, the significant group interaction in the right HS showed that there was a tendency towards a positive relationship in YA and a negative relationship in OA ($\beta=-.51$, $p=.005$). Lower SNR ($F(3,32)=4.90$, $p=.006$, $R^2_{corr}=.25$) was predicted by a bigger mean CSA in left POP ($\beta=-.56$, $p=.001$).

There were no significant regressions using the control regions (visual cortex and somatosensory cortex) as predictors (all p 's $> .77$) underlining the specificity of the significant predictors to hearing.

3.5. Associations between anatomy and theta and gamma lateralization

In the regression analysis for the OA, we found that a thicker right STS ($\beta=-.48$, $p=.023$) predicted more rightward lateralization of theta power in resting state ($F(1,20)=6.04$, $p=.023$, $R^2_{corr}=.19$) (see Figure 6A) while this effect was not found in younger adults ($F(1,11)=.14$, $p=.72$, $R^2_{corr}=.01$). For the lateralization of gamma in resting state EEG, no significant predictor was found, neither in the YA ($F(1,12)=.45$, $p=.51$, $R^2_{corr}=-.05$), nor in the OA ($F(1,20)=1.63$, $p=.22$, $R^2_{corr}=.03$).

Overall, we found lower auditory performance in older compared to younger adults, independent of peripheral hearing loss. This behavioral pattern in older adults was accompanied by lower CT in all ROIs defined for this work, and also by intrinsic right-

lateralized theta power. Furthermore, lower CT in right auditory areas was associated with lower performance and less lateralized theta power in older adults only.

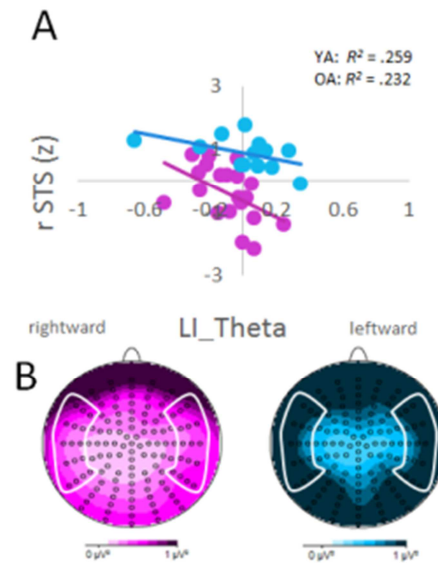


Figure 6(A) shows the significant results of the multiple regression analyses with the lateralization of theta power as an outcome variable and the CT of all eleven bilateral ROIs as predictors. We found that a thicker right STS ($\beta = -.48$, $p = .023$) predicted more rightward lateralization of theta power in resting state ($F(1,20) = 6.04$, $p = .023$, $R^2_{corr} = .19$) only in OA, while this effect was not found in YA ($F(1,11) = .14$, $p = .72$, $R^2_{corr} = .01$). Note also that theta power was only in OA significantly right-lateralized, but not in YA. Figure 6 (B) shows the topographies for theta (3-7 Hz), for the older adults on the left and for the young adults on the right.

4. Discussion

The aim of this study was to describe neuroanatomical and functional underpinnings of auditory perception and speech processing difficulties experienced by healthy, older adults with normal peripheral hearing as indicated by the audiogram. We therefore examined a sample of young and older participants and analyzed supra-threshold auditory and SiN tasks, as well as anatomical and intrinsic auditory-related EEG data. The current study sheds light on the interrelationship between neuroanatomical parameters and lateralized theta and gamma power, thus yielding a more comprehensive view of the neuroplastic causes of central hearing loss in older adults.

4.1. Peripheral hearing loss does not explain above-threshold auditory perception deficits in older adults

In line with our hypotheses, older adults performed worse than younger in both temporal (see Figure 3B, C) and spectral (see Figure 3A, C) adaptive hearing tasks. Thus, despite the older adults having audiograms which would not signal peripheral hearing loss when tested in clinics, we still found deficits in their auditory and speech processing. This finding is in line with previous studies (Füllgrabe, 2013; Füllgrabe et al., 2015; Hopkins and Moore, 2011; Vermeire et al., 2016) and highlights the existence of a central hearing loss, which may act independently of peripheral hearing. Older adults also performed worse in the SiN test. The lower performance in the SiN is an important replication of former studies (Fostick et al., 2013; Wong et al., 2008, 2009; Patrick C. M. Wong et al., 2010) and strengthens the assumption that older adults labelled as peripherally normal hearing appear to have difficulties perceiving speech within a noisy background. This result also resembles that of Vermeire and colleagues (2016), who used a very similar method in their evaluation of younger and older adults' abilities to understand speech-in-noise. The sum of evidence showing lower performance of older adults in SiN tasks reinforces the idea outlined above, namely that age rather than peripheral hearing loss per se, adversely influences speech processing, especially within the context of interfering background noise (Profant et al., 2014). Taking these findings and the present data into account, it seems to be reasonable to claim that peripheral hearing ability as shown in the audiogram plays only a secondary role in central speech processing difficulties. We think that these findings have important implications for clinics and future research. Clearly, traditional pure-tone threshold testing does not comprehensively describe an older person's hearing ability. Rather, tests that are sensitive to central and cognitive hearing, such as introduced here, should be applied to understand the individual's hearing acuity.

4.2. Central hearing loss: Emerging through age-related cortical thinning?

In line with our hypotheses, we found age-related cortical thinning in auditory areas unrelated to hearing thresholds, namely in the right PP, the bilateral PT, STG, STS, HG, and HS. Furthermore, higher-order regions involved in speech processing such as the bilateral dlPFC, inferior frontal gyrus, and PCUN were also shown to be thinner in the

older participants than in the younger adults (see Figure 4A). This result is consistent with the major findings of previous studies showing that aging affects brain morphology negatively, also in auditory areas (Fjell et al., 2009, 2014; Hogstrom et al., 2012; Profant et al., 2014; Raz et al., 1997; D. H. Salat et al., 2004; Sowell et al., 2003; Patrick C. M. Wong et al., 2010). As expected, we did not find age group differences in CSA of the same cortical regions (see Figure 4B), an observation which accords with the literature (Profant et al., 2014) and the radial unit hypothesis (Rakic, 1988, 1995). In agreement with the research of Storsve and colleagues (2014b), the nonexistent age contrast in CSA underlines the distinguishable lifespan plasticity of CT and CSA. Moreover, it has been stated that CT and CSA have different genetic sources (Panizzon et al., 2009). According to the radial unit hypothesis (Rakic, 1988, 1995), there is no genetic relationship between the two parameters. Whereas CSA has been shown to be related to the number of columns, CT has been related to the number, packing density, and size of cells within a column (Rakic, 1988, 1995, 2007). In other words, aging may lead to a loss of dendritic branching in the auditory and higher areas involved in language, whereas the number of columns remains relatively stable across the lifespan. Our results therefore emphasize the importance of discriminating between CT and CSA in future studies (Amlie et al., 2016; Lee et al., 2016; Lyall et al., 2015; Panizzon et al., 2009; Rakic, 1988, 1995).

To elucidate if age-related cortical thinning in older adults is a factor contributing to the complex emergence of central hearing loss, multiple regressions with CT as predictors were calculated. Indeed, we showed several statistically significant relations between CT and auditory performance (see Figure 5A). Regardless of age, CT of the left dlPFC was predictive of FS. Regarding SiN performance, CT of the left POR and the left PTRI as well as CSA of the left POP, which are all areas of the ventrolateral frontal lobe, which has been shown to be activated during SiN processing (Bidelman and Howell, 2016), were predictors. In the context of auditory processing, the PFC has been attributed to “top-down” control (Miller and Cohen, 2001), for example, when participants need to selectively attend to one feature. Such is the case in the speech-in-noise test, in which success involves selectively attending the speech signal while ignoring the background noise, a phenomenon that has previously been shown to correlate with higher CV in the PFC in older adults (Patrick C. M. Wong et al., 2010). This relationship between “top-down” control and performing well in the SiN is further supported by a study which used structural equation modelling to demonstrate that some variance of SiN performance in

older adults can be explained by auditory working memory, auditory short-term memory and auditory attention (Anderson et al., 2013b).

Besides the PFC, we also found a positive relation between CT of another non-auditory region, namely the visual cortex, and performance in hearing tasks. Interestingly, it has been shown that visual activation can be present during different kinds of hearing tasks (Giraud and Truy, 2002) and that the expectation of visual cues (e.g., lip reading) activates visual areas in hearing impaired cochlear implant users, probably because they rely more strongly on visual information in everyday life (Giraud et al., 2001). Furthermore, there is evidence of visual activity in audiovisual tasks, which increases when the auditory input is distorted (Schepers et al., 2015). Moreover, hearing aid users who received audiovisual training (Yu et al., 2017) and normal hearing adults who learned American Sign Language (ASL) as a multisensory training (Williams et al., 2016) showed increased use of lip reading after the training and at the same time increased connectivity between auditory and visual cortices. All this evidence together therefore suggests that during difficult hearing situations, even in the absence of visual cues, the visual cortex may play a role in hearing. Thus, we infer that the relations between CT of the visual cortex, a measure for visual plasticity across the lifespan, and hearing, reflects structural reorganization of the visual cortex as a function of slowly developing central hearing loss across the lifespan.

Interestingly, age modulated several relationships between CT and auditory acuity (see Figure 5A). We found that these correlations were mainly positive. However, we consistently found stronger effect sizes in older than in younger adults. Assuming higher CT reflected more cell density and synapses (Rakic, 1988, 1995, 2007), then one conclusion that can be drawn from this finding is that, when growing older, the more cell density and synapses an older person already has in auditory and speech relevant areas, the less central hearing loss this individual will experience. More precisely, higher CT in the right PT predicted better spectral performance, while higher CT in the right HS related to better temporal and SiN performance. Furthermore, we found that larger CSA in right HG and right STG predicted better FS, while higher CSA in the left PP and the left HS, together with the right STG, related to better TC. These lateralized relations between auditory areas and auditory performance might be explained by the theory of Zatorre and Belin (2001), which postulates that auditory-related areas of the right hemisphere are

specialized in the processing of spectral information, whereas the left hemisphere is more responsible for temporal processing of acoustic signals. Accordingly, as far as the connection between CT of the right PT and spectral performance is concerned, the finding is in line with the framework. However, there was a finding that went against the predictions in that TC was also related to right auditory areas, namely to the right HS. When consulting the regressions using CSA, Zatorre and Belin's model has a partially better fit. Notably, this theory was based mainly on functional data and, furthermore, specialized to younger adults only. Thus, we have to consider that aging might modulate the predicted specialization of right and left auditory areas (Profant et al., 2015). Because of its higher percentage annual change, the parameter expected to change across the lifespan would be CT, rather than CSA (Storsve et al., 2014b). This is in line with our results showing no age differences in CSA. In particular, CSA seems to better reflect speech organization as predicted by Zatorre and Belin's model (Robert J. Zatorre and Belin, 2001), while CT might reflect age-related differences. If this hypothesis holds true, we can infer from our data that CT of the structural integrity of the right auditory areas specifically, becomes more important for a variety of auditory tasks across the lifespan, despite a general decline in both the left and right auditory areas. We therefore conclude that cortical thinning in the right auditory areas may play a significant role in central hearing loss. In order to relate these findings to functional auditory organization, we calculated multiple regressions of CT in auditory areas to predict the intrinsic functional lateralization of these areas.

4.3. Right-lateralization of theta power in older adults – a signal for the importance of prosodic perception in older adults?

In order to understand central hearing loss comprehensively, we investigated further the relationship of the cortical thinning in auditory regions of older adults with EEG theta and gamma band power lateralization, particular to the intrinsic organization of speech (Giraud et al., 2007; Morillon et al., 2012). According to the AST framework by Poeppel (2003a), a rightward theta lateralization and a leftward gamma lateralization can be expected; these are imprinted in the intrinsic oscillatory activity in younger adults (Giraud et al., 2007; Giraud and Poeppel, 2012a; Morillon et al., 2012; Poeppel, 2001, 2003a). On the topography (see Figure 6B), our findings of a rightward lateralization of theta power in older adults, but not in younger adults, contrasts with

the literature (Giraud et al., 2007; Morillon et al., 2012). Methodological differences may account for this age group discrepancy, as both previous studies worked with a higher spectral resolution, using simultaneous EEG-fMRI (Giraud et al., 2007) and depth electrodes (Morillon et al., 2012). Nevertheless, the functional preference of the right auditory areas towards slowly changing acoustic cues, and therefore prosodic and intonation patterns, in the speech signal seems to become more important in older adults. This finding is supported by a number of behavioral studies demonstrating that older adults, in comparison to younger adults, have more difficulties with rapidly changing cues. Such cues can comprise phonetic discrimination or temporal fine structure in speech (Gordon-Salant et al., 2010, 2015; Gordon-Salant and Fitzgibbons, 1999; Schneider and Pichora-Fuller, 2001). In contrast, prosodic perception remains relatively stable across the lifespan and has even been shown to play a supporting role in the syntactic parsing of sentences (Steinhauer et al., 2010) and their later recall (Wingfield et al., 1992, 2000), a process that is implemented via neural oscillations (Kreiner and Eviatar, 2014). The theta power lateralization was further related to a thicker right STS (see Figure 6), a relation that was only significant in older adults. First, this correlation shows that higher structural integrity of the right auditory areas is related to a rightward lateralization of theta power, which may imply the above described strong use of suprasegmental cues in speech. Thus, future studies should test whether less cortical thinning in right auditory areas is also directly related to a rightward lateralization of theta during online suprasegmental processing and not only during resting state. Second, the fact that it was the CT in the right STS that predicted the theta lateralization, matches reasonably well to previous studies which showed that the STS is specifically tuned to the temporal structure of speech, parsing segments of up to 500 ms, and therefore entraining to slowly changing acoustic cues (Boemio et al., 2005; Overath et al., 2015). Besides the fact that there were no hemispheric differences in the temporal preferences of the STS (Overath et al., 2015), its role during the processing of slowly temporal speech cues supports the reasoning outlined above, and is line with the AST model.

4.4. Implications for current neurofunctional theories about aging

The hemispheric asymmetry reduction in older adults (HAROLD) model suggests that prefrontal activity is more bilateral, and therefore less lateralized, in older adults

when cognitive performance is comparable to that of younger adults (Cabeza, 2002; Cabeza et al., 2002; see also Grady, 2012; Reuter-Lorenz and Park, 2010 for a discussion of the model). Such bilateralization was interpreted as a neurofunctional dedifferentiation occurring with age. However, in this current work, we found more lateralization of theta in older adults compared to younger adults. This may be because, in contrast to the HAROLD model, we investigated structural data (not functional) and did not directly calculate lateralization. Nevertheless, the fact that cortical thinning in only the right auditory areas predicted the extent of central hearing loss in older adults could indicate a structural differentiation of their left and right auditory areas.

The HAROLD (Cabeza, 2002; Cabeza et al., 2002) model does not stand alone; the PASA model also predicts changes of prefrontal activity in older adults. Davis et al. (Davis et al., 2008) found that older adults tend to intensively use the (pre)frontal areas that provide additional top-down controlled resources for episodic memory and visual perception tasks. The authors called this stronger activation in (pre)frontal areas posterior-anterior shift in aging (PASA). Indeed, using a SiN task, it has been demonstrated that there is reduced activity in the bilateral posterior superior temporal gyri of older adults accompanied by an increase of activity in the prefrontal and posterior parietal cortex compared to younger adults (Wong et al., 2009). In contrast, our anatomical results did not show stronger correlations between the frontal regions and behavioral performance, but rather stronger correlations in the right auditory areas. However, the assumption that brain atrophy with increasing age is more pronounced in frontal areas than auditory regions (Abe et al., 2008; Allen et al., 2005; Lemaitre et al., 2012; Raz et al., 1997; Tisserand et al., 2002), renders a possible compensation within this region questionable. It is therefore important to carefully investigate and discuss the underlying reason for a frontal over-activation in older adults during speech processing (Du et al., 2016).

4.5. Limitations

In this study we investigated anatomical MRI and task-free EEG data to explain central hearing loss. All auditory tasks were acquired in a separate session, and not directly during EEG recording. In future studies, the intrinsic electrophysiological organization should be studied together with the behavioral testing in order to observe

how an older brain activates during an auditory task. However, the present work was designed to study the intrinsic anatomical and functional organization of auditory areas in the aging brain. The fact that, to date, studies aiming to describe intrinsic speech-relevant oscillatory lateralization have used only younger adults, shows that our approach complements present work.

Another limitation concerns the cross-sectional nature of this study. Naturally, it is not feasible to draw conclusions about the directions of effects. In particular, it would be interesting to study whether stronger peripheral hearing loss would affect central hearing loss, and how both types of hearing loss interact, or if they are just correlated because of a common, age-related cause. Furthermore, using central hearing as an outcome, it would be interesting to study the longitudinal effects of peripheral hearing or hearing aids as predictors for neural plasticity (Giroud et al., under review, 2017). Nevertheless, the current study pointed to important age-related differences in anatomical and intrinsic functional organization, which could serve as a baseline for longitudinal studies.

In addition, our younger and older adults differed in their peripheral hearing as assessed by the pure tone thresholds. The inclusion of older adults with pure tone thresholds up to 30 dB was motivated by the fact that thresholds up to 30 dB seem to be the age-typical for the healthy older adults screened for this study. It was not possible to find older adults with thresholds as low as those found in younger adults. In the context of this work, these age-related differences in peripheral hearing were counterbalanced by the central hearing tests which were corrected for the individual thresholds. Future studies should furthermore investigate whether there are some forms of hidden hearing loss present in the cochlea (Bharadwaj et al., 2014; Plack et al., 2014) which are not necessarily evident in the audiogram. However, a standard definition and standard procedure to assess hidden hearing loss in humans has first to be established.

4.6. Conclusion

In our increasingly aging society, age-related hearing loss is a very common disease, but one which is often ignored. In many cases, hearing aids do not seem to completely overcome the difficulties around understanding speech. Such difficulties are frequently reported by older adults with central hearing impairments, and even by

individuals with peripherally normal hearing. Eventually, these deficits in communication can have a negative impact on social interactions and the quality of life of the people affected. This stark reality reflects the absolute necessity of finding complementary treatments based on biomarkers from which to evaluate central hearing loss. The results from the present study might help towards better understanding both the hearing difficulties of older citizens and how central hearing loss emerges. First, the present study substantiated the assumption that impaired speech processing cannot be explained solely by elevated hearing thresholds. Second, age-related differences in cortical morphology demonstrate that, next to peripheral damage, the anatomy of the aging central nervous system needs to be taken into account. For instance, we showed that older adults demonstrated thinner auditory and higher-order cortices relevant for speech processing. However, age mainly modulated the relation between the extent of cortical thickness in right auditory areas (Heschl's sulcus, planum temporale) and auditory performance. More precisely, thicker right auditory areas may become more important for speech processing across the lifespan. Third, the right-lateralized intrinsic theta power is further pointing to the relevance of slowly changing cues in speech signals for older adults. This work therefore provides new insights for future developments in the treatment and rehabilitation of auditory perceptual difficulties in older adults and extends present frameworks of age-related hearing loss by suitably combining EEG/structural MRI and behavior.

2.2. Study II: Longitudinal Auditory Learning Facilitates Auditory Cognition as Revealed by Microstate Analysis

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Abstract

The current study investigates cognitive processes as reflected in late auditory-evoked potentials as a function of longitudinal auditory learning. A normal hearing adult sample (n=15) performed an active oddball task at three consecutive time points (TPs) arranged at two week intervals, and during which EEG was recorded. The stimuli comprised of syllables consisting of a natural fricative (/sh/, /s/, /f/) embedded between two /a/ sounds, as well as morphed transitions of the two syllables that served as deviants. Perceptual and cognitive modulations as reflected in the onset and the mean global field power (GFP) of N2b- and P3b-related microstates across four weeks were investigated using microstate analysis. We found that the onset of P3b-like microstates, but not N2b-like microstates decreased across TPs, more strongly for difficult deviants leading to similar onsets for difficult and easy stimuli after repeated exposure. The mean GFP of all N2b-like and P3b-like microstates increased more in spectrally strong deviants compared to weak deviants, leading to a distinctive activation for each stimulus after learning. Our results indicate that longitudinal training of auditory-related cognitive mechanisms such as stimulus categorization, attention and memory updating

processes are an indispensable part of successful auditory learning. This suggests that future studies should focus on the potential benefits of cognitive processes in auditory training.

1. Introduction

There is a substantial body of research providing evidence for neuroplastic changes in the human auditory central system as a function of auditory experience. Neurofunctional auditory plasticity can be measured by recording auditory evoked potentials (AEPs) over the scalp. AEPs assess voltage fluctuations arising from acoustic stimulation. For instance, lifelong musical training has not only been shown to improve behavioral auditory performance, but also to modulate AEPs (Baumann et al., 2008; Kühnis et al., 2013a, 2014; Kuriki et al., 2006; Marie et al., 2011; Shahin et al., 2003, 2005). In fact, even short-term auditory training in non-musicians has been shown to change auditory brainstem responses and central AEPs, such as the N1/P2 complex or the mismatch negativity (MMN) (Anderson et al., 2013a, 2013c, 2014; Bosnyak et al., 2004; Reinke et al., 2003; Ross et al., 2013; Sheehan et al., 2005; Tremblay et al., 1997, 2001, 2010, 2014a; Tremblay and Kraus, 2002). For example, a previous study focused on AEP plasticity by applying a six-day training design with pre- and post-testing. The authors found that participants who learned to identify 10 ms intervals of the voice onset time (VOT) in syllables showed increased N1/P2 peak-to-peak amplitudes after training (Tremblay et al., 2001). This discovery was confirmed by another study, which showed that listeners, who received a week's training in learning to identify vowels, showed decreased N1 and P2 latencies as well as enhanced P2 amplitudes when compared to untrained listeners (Reinke et al., 2003). Improvement of behavioral scores in perception were in both studies accompanied by P2 amplitude increases, which were attributed to a recruitment of neighboring cells (Reinke et al., 2003) or to an increased neural synchrony (Tremblay et al., 2001) responding to practiced stimuli. All this compelling evidence for functional auditory plasticity notwithstanding, there are still several open questions regarding the brain-behavior relationship between AEP amplitudes and auditory learning.

The present study seeks to contribute to this discussion by addressing the following issues: First, the effects of behavioral auditory learning on cognitive neural processes have not been particularly addressed. Previous work showed that repeated auditory exposure changed the early perceptual processing of speech (Anderson et al., 2013a, 2013c, 2014; Bosnyak et al., 2004; Reinke et al., 2003; Ross et al., 2013; Sheehan et al., 2005; Tremblay et al., 1997, 2001, 2010, 2014a; Tremblay and Kraus, 2002).

Surprisingly, none of these studies investigated later AEPs for measuring plasticity in auditory cognition as a function of repeated auditory exposure. Thus, up to date, the full extent of auditory plasticity has not yet been established. In other words, it is unclear whether auditory stimulation merely affects perceptual plasticity as reflected in early AEPs or whether it can also facilitate cognitive plasticity as reflected in later AEPs. Previous studies fall short of specifying the nuances of this relationship, by suggesting only a strong correlation between auditory-based cognitive training and brainstem responses to speech (Anderson et al., 2013a, 2013a, 2014). We therefore investigated the influence of repeated auditory stimulation on neural processes such as the N2b/P3b AEP complex as evoked by target stimuli in active oddball paradigms. The active oddball paradigm allows for the exploration of perceptual as well as cognitive auditory processes at the same time, with the N2b component being a perceptual neural marker which occurs when the stimulus is attended and categorized as a deviant (Näätänen and Gaillard, 1983; Simson et al., 1977), and the P3b component being a cognitive neural marker for subsequent memory processing and updating (Debener et al., 2002; Kok, 1997; Polich, 2007; Volpe et al., 2007).

Second, with regard to the longitudinal time course of auditory learning, it has yet to be established how auditory learning and its underlying neural parameters change across several learning stages. Previous studies have so far only applied a pre-post design to investigate primarily the improvements between two time points and the stabilization in a follow-up measurement (Bosnyak et al., 2004; Reinke et al., 2003; Ross et al., 2013; Sheehan et al., 2005; Tremblay et al., 1997, 2001, 2010, 2014a; Tremblay and Kraus, 2002). However, it has been shown that early and later AEPs can have different time courses of learning stages with the P2 increasing faster than the MMN (Atienza et al., 2002). Further, behavioral and neural time courses may differ which can only be detected by using more than two measurement time points (Tremblay et al., 1998). Thus, in the present study we used three time points of data acquisition (TPs) with an interval of two weeks between each in order to study the time course of behavioral and cognitive-related auditory plasticity. At each TP, participants performed the same three randomized stimulus blocks, each consisting of a standard stimulus and three deviants, while EEG was recorded.

Third, the stimulus material consisted of morphed continua of vowel-consonant-vowel (VCV) syllables creating three difficulty levels of deviants. Thus, each stimulus block consisted of an easy (strong deviant), moderate (moderate deviant) and a difficult (weak deviant) deviant stimulus (DEVs). This allowed for the additional study of auditory learning at various difficulty levels, an approach which was emphasized only in cross-sectional studies (Berti et al., 2004; Falkenstein et al., 1994; Ferdinand et al., 2008, 2015; Katayama and Polich, 1998; Novitski et al., 2004; Rogenmoser et al., 2014; Rüsseler et al., 2003). This previous work showed that stimulus difficulty tremendously affects the N2b/P3b ERP complex in a way that stronger acoustic deviation from the standard resulted in increased amplitudes and decreased latencies.

Taking these three points into account, the present study utilized a topographical analysis approach because previous evidence has shown different effects of repeated stimulus exposure dependent on the selection of electrodes. For example, enhanced P2-amplitudes over right temporal sites were found in both, a vowel-identification training group and an untrained control group, while the increased P2-amplitudes were specific for the training group over central and left temporal electrode sites only (Reinke et al., 2003). Thus, if not for a multi-electrode approach, these differences could not have been detected. It is therefore of the utmost importance to provide an alternative approach that replaces single electrode based analysis which is biased by the observer. An innovative topographical ERP approach allows for the consideration of all recorded electrodes and avoids the manual choosing of electrodes or electrode pools. In addition, topographical ERP measures are reference independent (Koenig et al., 2014; Lehmann and Skrandies, 1980, 1984). Furthermore, when applying the standard ERP approach careful consideration needs to be given to the definition of the time windows. By using a cluster analysis, the topographic signal can be analyzed in a data-driven manner without an arbitrary a priori definition of time windows. The microstate approach (Koenig et al., 2014; Murray et al., 2008) provides a temporal clustering of the topographical configurations, and segments the ERP time course into temporally stable topographies (so-called microstates), which can be described by parameters such as onset and mean global field power (GFP). These microstates have also been shown to correspond to ERP components (Michel et al., 2009). The use of EEG as an established functional imaging method can also be summarized as electrical neuroimaging (Michel et al., 2009b).

On a behavioral level, we expected to find better performance for easy compared to difficult DEVs, consistent with previous findings (Gaál et al., 2007; Johnson, 1986; Katayama and Polich, 1998; Kok, 1997) and expected this to be accompanied by higher GFP and shorter onsets¹ of the N2b/P3b complex (Gaál et al., 2007; Johnson, 1986; Katayama and Polich, 1998; Kok, 1997). In case that repeated auditory testing drives not only perceptual plasticity as shown in previous studies (Anderson et al., 2013a, 2013c, 2014; Bosnyak et al., 2004; Reinke et al., 2003; Ross et al., 2013; Sheehan et al., 2005; Tremblay et al., 1997, 2001, 2010, 2014a; Tremblay and Kraus, 2002), but also cognitive plasticity, one would expect to find longitudinal changes in the P3b component, especially for the difficult DEV. Alternatively, if auditory learning is mainly driven by perceptual processes, effects are more likely to be associated with changes in the N2b. Moreover, we expected to find GFP increases and onset decreases first, in line with a previous study suggesting that changes in neurophysiology may precede changes in behavior (Tremblay et al., 1998).

2. Materials and Methods

2.1. Participants

The sample comprised 15 adults (mean age = 40.6 years, SD = 7.4, 8 women) with an age range from 28 to 52 years. All participants but one were right-handed, as indicated by standard handedness questionnaires (Annett, 1970b; Bryden, 1977). All participants were native German or Swiss German speakers. None of them reported any history of present or past neurological, psychiatric, or neuropsychological disorders. They denied the consumption of drugs or illegal medications and none suffered from chronic tinnitus. Furthermore, all participants had a normal IQ (mean IQ = 118.64, SD = 12.64, range = 103-140) as measured with the KAI intelligence test (Lehrl, 1992).

The local ethics committee of the University of Zurich approved the study, and written informed consent was obtained from all participants. Participants were paid for their participation.

¹ For the sake of convenience, we will compare the mean GFP and the onset results from the current study with the peak amplitude modulations and peak latency changes respectively from previous studies.

2.2. Hearing abilities

The online digit triplets test (Buschermöhle et al., 2014, 2015) was used to measure the hearing accuracy of the participants. The digit triplets used for the test were recorded by a trained female speaker. Each digit was one of nine monosyllabic digits between zero and nine. The disyllabic digit seven was excluded. The triplets were presented to the participants via headphones. After each trial, participants were asked to indicate which digits they had heard by entering those digits into the computer. The stimuli were always presented with background noise that had a fixed volume, while the triplet volume was varied adaptively. The adaptive procedure allowed us to determine the signal-to-noise ratio (SNR) that corresponds to 50% intelligibility of the triplets. The final results were presented in three categories of hearing acuity (good: SNR loss < 2.9 dB, insufficient: 2.9 dB < SNR loss < 5.6, and poor: 5.6 < SNR loss) (Smits et al., 2006). This test was shown to be sensitive for (sensorineural) hearing loss (Smits and Houtgast, 2007), and therefore also facilitates the screening of normal hearing participants. To pass this test, participants were required to have an SNR loss smaller than 2.9 dB for both ears.

The online digit triplets test is part of the European HearCom project (Vlaming et al., 2011) and is available at <http://hearcom.eu/main.html>. Eleven participants were tested with the German version (Zokoll et al., 2012) and four participants were tested with the English version, because the German version was occasionally not available online.

2.3. Stimulus material

Three syllables from the phoneme perception test (Boretzki et al., 2011) were used as stimulus material (see Figure 1). This stimulus material was recorded by a trained female speaker with a fundamental frequency of 180 Hz and with a sampling rate of 44.1 kHz and a sampling depth of 32-bits. All syllables used in this study consisted of an initial /a/ (length 240 ms) and a final /a/ (length 290 ms) sound. A consonant (length 140 ms) was embedded between the two vowels. In the first syllable, the alveolar /s/ (/a:sa/) was used, in the second syllable the post-alveolar /sch/ (/a:ʃa/), and in the third syllable the labiodental /f/ (/a:fa/). The middle consonants were therefore unstressed fricatives. The frequency of the /s/ was centered at 7.65 kHz,

the frequency of the /ɜ:/ was centered at 3.14 kHz and the frequency of the /ɜ:f/ was centered at 11.03 kHz.

Further stimulus material was created based on these syllables. By using a morphing algorithm (Zorn, 2000), two equidistant intermediate acoustic steps between the syllables /ascha/-/asa/, /afa/-/asa/, and /ascha/-/afa/ were created, respectively, resulting in a total of 9 different stimuli. Pitch, energy, spectrum and rhythm were morphed, and further to this, equidistant intermediate steps of these four parameters between the two signals were calculated.

With respect to the oddball paradigm, the stimulus material was divided into three blocks as will be described in the following.

2.3.1. Block 1: Ascha-Asa

In Block 1, we defined the original ascha (/ʼa:ʃa/) as the standard stimulus, while the two morphed stimuli (DEV 1 and DEV 2) and the original asa (/ʼa:sa/) (DEV 3) were defined as the three deviant stimuli. DEV 1 had only a slight acoustic deviation from the standard stimulus and was therefore the hardest to identify. DEV 2 was a moderate deviant, and DEV 3 was the strongest deviant, which made it the easiest to recognize. Thus, the three deviant stimuli differed in their acoustic deviation from the standard, and as a result, also in their detection difficulty.

2.3.2. Block 2: Ascha-Afa

For the second block we also used the original ascha (/ʼa:ʃa/) as the standard stimulus (just as in Block 1), but the two morphed stimuli (DEV 1 and DEV 2) with the afa (/ʼa:fa/) (DEV 3) made up the deviant stimuli. As was described for Block 1, DEV 1 was the hardest to detect, while DEV 2 was moderate and DEV 3 was easy.

2.3.3. Block 3: Afa-Asa

In this block the original afa (/ʼa:fa/) was used as the standard stimulus, while as in Block 1, the two morphed stimuli (DEV 1 and DEV 2) together with the asa (/ʼa:sa/) (DEV 3) were the deviant stimuli. As before, DEV 1 was the most difficult deviant, DEV 2 was moderate and DEV 3 was an easy deviant. We refrain from reporting the results of

this block to avoid redundancy, because the behavioral performance showed the same pattern as Block 1.

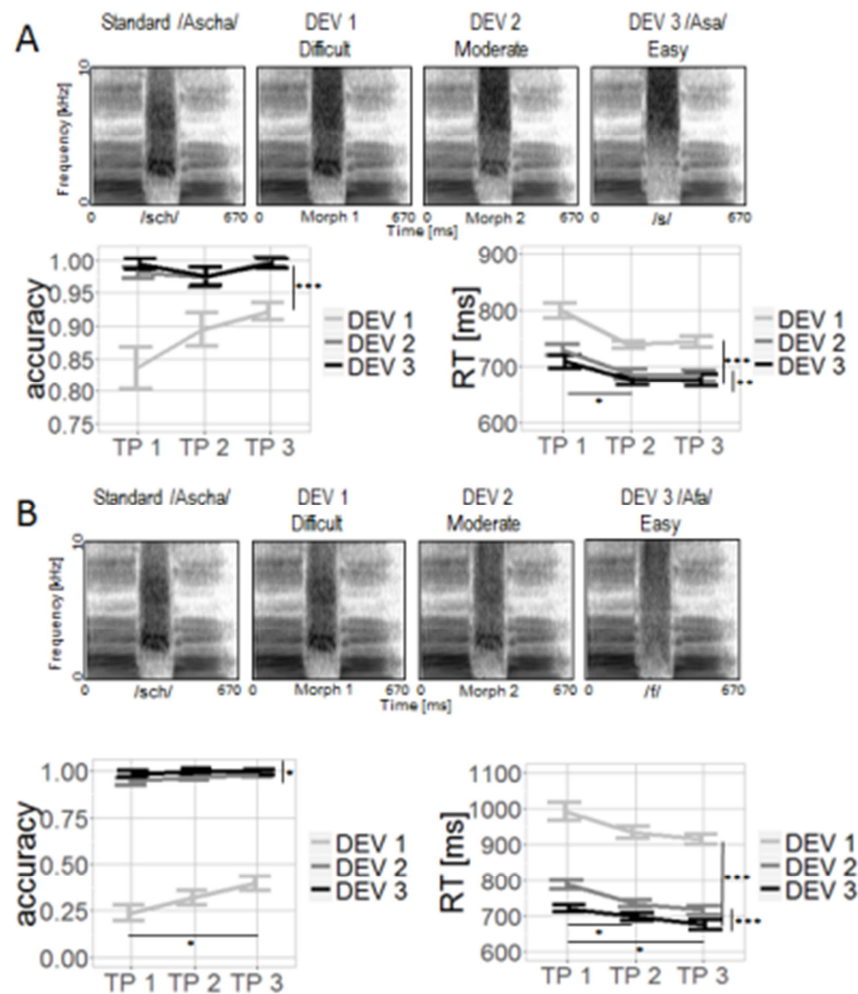


Figure 1: This figure depicts the stimulus material and the behavioral results of the stimulus block Ascha-Asa **(A)** and the stimulus block Ascha-Afa **(B)**. **(A)** The spectrograms of all four stimuli of the block Ascha-Asa are depicted. The standard stimulus contains the token ascha (/ʼa:ʃa/) and the DEV 3 contains the acoustic signal of the token asa (/ʼa:sa/). The spectrograms of the DEVs 1 and 2 show the two morphed intermediate steps between the standard stimulus and the DEV 3. Furthermore, this figure depicts the percentage of correct responses (accuracy) and the reaction time in the oddball detection task as a function of TP and DEV. **(B)** The spectrograms of all four stimuli of the block Ascha-Afa are shown. The standard stimulus contains the token ascha (/ʼa:ʃa/) and the DEV 3 contains the acoustic signal of the token asa (/ʼa:fa/). The spectrograms of the DEVs 1 and 2 show the two morphed intermediate steps between the standard stimulus and the DEV 3. Moreover, this figure depicts the percentage of correct responses (accuracy) and the reaction time in the oddball detection task as a function of TP and DEV. Error bars indicate the standard errors (SE) and * depicts $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$.

2.4. Experimental procedure

The EEG recordings were made for three appointments in total. The participants were invited for the first recording (TP 1) and were retested two weeks (TP 2) and four weeks (TP 3) after TP 1. Each TP was scheduled at the same time of day to control for changes in attention during the day.

Participants were seated in a comfortable chair in front of a screen, at a distance of 75cm in front of the speaker. As the paradigm used should also be applicable in studies of individuals who wear hearing aids, we tested the usage of speakers rather than headphones for the stimulus presentation. The participants were instructed to look at a fixation cross, which was presented on the screen during the EEG measurement in order to avoid eye movement artifacts during data acquisition. Each participant performed two runs containing the three blocks each. Each block lasted about nine minutes and was followed by a short pause before the start of the next block. The three blocks contained different sets of stimulus material as described above. Their order was randomized between participants and between TPs.

The standard stimulus of each block was presented 270 times ($p = 0.75$), while the three DEVs were each presented 30 times (each $p = 0.083$) in a randomized order. The block started with a sequence of at least six successive standard stimuli in order to create a memory trace. The inter-stimulus interval was set to 730 ms. The presentation of the auditory stimuli was controlled by Presentation software (www.neurobs.com; version 14.5). Participants were instructed to listen to the stream of stimuli and to press the mouse button with the right index finger whenever a DEV stimulus appeared. All trials of one block were analyzed together, resulting in 60 trials per DEV and 540 trials for the standard stimulus for each block.

All stimuli were presented at a volume of 65 decibels (dB) which was not a trivial issue: A behavioral pilot study showed that the three fricatives /s/, /ʃ/ and /f/ were not perceived as equally loud at the volume level of 65 dB. It was therefore possible that participants had pressed the target button as a reaction to perceived differences in loudness rather than perceived differences in the quality between the standard stimulus and the DEV stimuli. To counter this possible bias, we measured the perceived difference in loudness of the token *asa* (/a:sa/), the token *ascha* (/a:ʃa/) and the token

(/’a:fa/) by instructing participants to set the volume level of the two stimuli manually to an equal loudness level. They were allowed to listen to all stimuli as many times as they wanted while setting the loudness level in 1 dB steps for the stimuli. If the objective volume was different at that point, a jitter in volume for the standard stimulus was introduced (a jitter of 1 dB if the difference between the two stimuli was 1 dB or a jitter of 2 dB if the difference between the two stimuli was 2 dB or more). This procedure prevented participants from detecting the DEVs due to perceived differences in volume rather than in phonetic cues.

A speaker (KEF, HTS2001.2, 8 Ω) with Uni-Q array technology was used to provide a single source of sound with a high quality frequency range of 80 Hz – 27 kHz and a maximum output of 104 dB. Furthermore, the use of this particular speaker technology completely eliminated the dip in the total energy output in the bass/treble crossover region of traditional speaker solutions, and it was also shielded to reduce the magnetic field output. To amplify the signal, a custom built 70V - 60W Dmos audio amplifier was used. Neither speaker nor amplifier had a significant electromagnetic influence on the EEG recordings. In every TP the volume for a sound of white noise was set to 65 dB using an audiometer (AL1 Acoustilyzer). A test-run of this set-up revealed that the acoustic attributes of our EEG chamber were inadequate for the use of speakers. The speaker created an echo, which resulted in multiple residual and delayed sound sources due to sound reflections off the chamber walls. To counter this, we partially isolated the chamber with 10 m² of white Basotec pyramid plates.

2.5. EEG recordings and preprocessing

EEG was continuously recorded using a high-density Geodesic EEG system (Electrical Geodesics, Inc., USA) with 256 scalp electrodes. Impedances were kept below 30 k Ω . The vertex electrode (Cz) served as the online reference. The data was digitized at a sampling rate of 500 Hz, and band-pass filtered between 0.1-100 Hz. Brain Vision Analyzer Software (Version 2.0.4, Brainproducts, Munich, Germany) was used for all pre-processing steps. The number of electrodes was reduced from 256 to 204 by removing the electrodes placed on the cheeks and the neck. The data was filtered offline between 0.1-20 Hz (24 dB/oct) and then re-referenced to linked mastoids for visual inspection of the grand averages at electrode Cz, and to average reference for further data analyses. Eye movements and eye blinks were removed using an independent

component analysis (ICA) (Jung et al., 2000). Other artifacts (e.g., movement artifacts) were removed with a semi-automatic raw data inspection, and noisy data at specific electrodes was interpolated (Perrin et al., 1987). The data was cut into 1100 ms segments (from 100 ms pre-stimulus to 1000 ms post-stimulus) and baseline corrected relative to the 100 to 0 ms pre-stimulus time period. All segments with correct detection of the DEVs were averaged for each participant, each DEV, and each TP in order to compute event-related potentials (ERPs). In addition, grand averages across all subjects were computed for each stimulus type and TP.

2.6. Topographic analysis of evoked activity: Microstate analysis

The microstate analysis, a topographical pattern analysis, can be used for evaluating temporally stable complex topographical configurations measured with high-density EEG (Pascual-Marqui et al., 1995). These stable intervals, the so-called microstates, have been shown to correspond to functionally relevant periods that are temporally and spatially related to the ERP components (Michel et al., 2009). The reasoning behind this is that scalp voltage potentials last for several tens of milliseconds in evoked activities before a change occurs in the configuration (Kühnis et al., 2013b; Murray et al., 2008). Microstates can be compared statistically between groups and conditions using their mean GFP and onset, while the mean GFP is defined as the standard deviation of the potentials at all electrodes of an average reference map averaged for one microstate (Skrandies, 1990). Thus, GFP is defined as

$$GFP = \sqrt{\frac{\sum_{i=1}^N (u_i - \bar{u})^2}{N}}$$

where u_i is the voltage of the map u at the electrode i , \bar{u} is the average voltage of all electrodes of the map u and N is the number of electrodes of the map u (Brunet et al., 2011). We computed a microstate analysis for the ERP time interval starting from 240 ms after stimulus onset at the onset of the deviation (the onset of the fricative) to 1000 ms after stimulus onset. In a first calculation step, a k-means algorithm was used to cluster spatially the grand averages of all conditions into stable time periods with Ragu software (version of 20. Jan 2015) operating on Matlab 2012b (The MathWorks Inc., Natick, MA, USA) (Koenig et al., 2011). The optimal number of microstates was evaluated with a cross-validation algorithm implemented in Ragu as follows (Koenig et

al., 2011, 2014): For each possible number of microstates ranging from 3 to 35, a subset of the data was chosen with 50 initializations and used to make predictions for the remaining data. The optimal model was defined as the one with the highest mean correlation between the two data sets. In a second calculation step, the grand averaged data of each condition was separately fitted back to the clustered microstates obtained by calculation step 1, by using randomization statistics (Koenig et al., 2011; Koenig and Melie-García, 2009). First, the effects of interest (i.e., onset and mean GFP) of each microstate were quantified. Second, the variances between the within-subject factors DEV (standard, DEV 1, DEV 2, DEV 3) and TP (TP 1, TP 2, TP 3) were computed for all effects of interest. Third, the data of the DEV and TP factors were repeatedly shuffled with 1000 repetitions (in order to obtain an α -level of 0.05). For each repetition the variance of all effects of interest was computed. The comparison between the distribution of the real variance and the distribution of the shuffled data then allowed for the assessment as to whether or not the probability of the observed difference between the DEV and TP factors for the effects of interest were compatible with the null hypothesis.

2.7. Analysis of behavioral data

The accuracy of the detection of the DEVs and the mean reaction time (RT) for correct trials was computed for each of the three DEVs for each TP and each subject. Afterwards, a 3x3 repeated mixed-measure analysis of variance (ANOVA) was conducted separately for the accuracy and the RT with TP (TP 1, TP 2, TP 3) and DEV (DEV 1, DEV 2, DEV 3) as within-subject factors. The ANOVAs were followed by bi-directional contrasts, when appropriate. The alpha level for all statistical analysis was set to $\alpha = 0.05$, with Bonferroni corrections if necessary. Effect sizes were indicated by partial eta-squares (η^2_p) (Hullelt and Levine, 2003).

3. Results

In the following results section, we will first describe the results for stimulus Block 1 Ascha-Asa and subsequently for stimulus Block 2 Ascha-Afa.

3.1. Results block 1: Ascha-Asa

3.1.1. Behavioral performance

With regard to the accuracy in oddball detection (see Figure 1A), repeated-measure ANOVAs revealed a main effect of DEV ($F(1.05,14.71)=42.88$, $p<0.001$, $\eta^2_p=0.75$) for accuracy, showing lower accuracy for DEV 1 than for DEV 2 ($p<0.001$) and DEV 3 ($p<0.001$) (DEV 1: M (Mean)=0.88 SD (Standard Deviation)=0.02, DEV 2: $M=0.98$ $SD=0.01$, DEV 3: $M=0.99$ $SD=0.01$). Our study did not find a main effect of TP nor an interaction between DEV and TP for accuracy (both $F_s<3.81$, both $p_s>0.05$). For the RTs (see Figure 1A), a main effect of DEV was found ($F(1.34,18.80)=121.04$, $p<0.001$, $\eta^2_p=0.90$), showing faster RTs for DEV 3 than DEV 1 ($p<0.001$) and DEV 2 ($p=0.003$), and faster RTs for DEV 2 than DEV 1 ($p<0.001$) (DEV 1: $M=760.78\text{ms}$ $SD=19.61\text{ms}$, DEV 2: $M=700.03\text{ms}$ $SD=17.63\text{ms}$, DEV 3: $M=686.63\text{ms}$ $SD=16.86\text{ms}$). Additionally, we found a main effect of TP ($F(2,28)=6.25$, $p=0.006$, $\eta^2_p=0.31$) with a faster RT at TP 2 than at TP 1 ($p=0.033$) (TP 1: $M=745.88\text{ms}$ $SD=18.88\text{ms}$, TP 2: $M=700.54$ ms $SD=19.23\text{ms}$, TP 3: $M=701.02\text{ms}$ $SD=21.10\text{ms}$). No interaction between DEV and TP was found.

3.1.2. Microstates

The topographic pattern analysis on the DEV and TP within-subject factors yielded four representative topographic scalp maps, which are depicted in Figure 2A, and their associated time course of the GFP is depicted in Figure 2B. The maps occur in the same temporal order in all DEVs and TPs: First, a N2b-like posterior negativity, then a N2b-like central negativity. After that, the frontal P3b-like frontal positivity occurs and then there is a longer interval with the P3b-like posterior positivity. Subsequently, the onset and mean GFP of these maps were subjected to the randomization statistics. Table 1 shows the descriptive data of these analyses, as well as the p-values for the main effect of TP, DEV and the interaction of TP * DEV. Additionally, Figure 4A shows the onset and the mean GFP of the stimulus block Ascha-Asa, separately for each microstate as a function of TP and DEV.

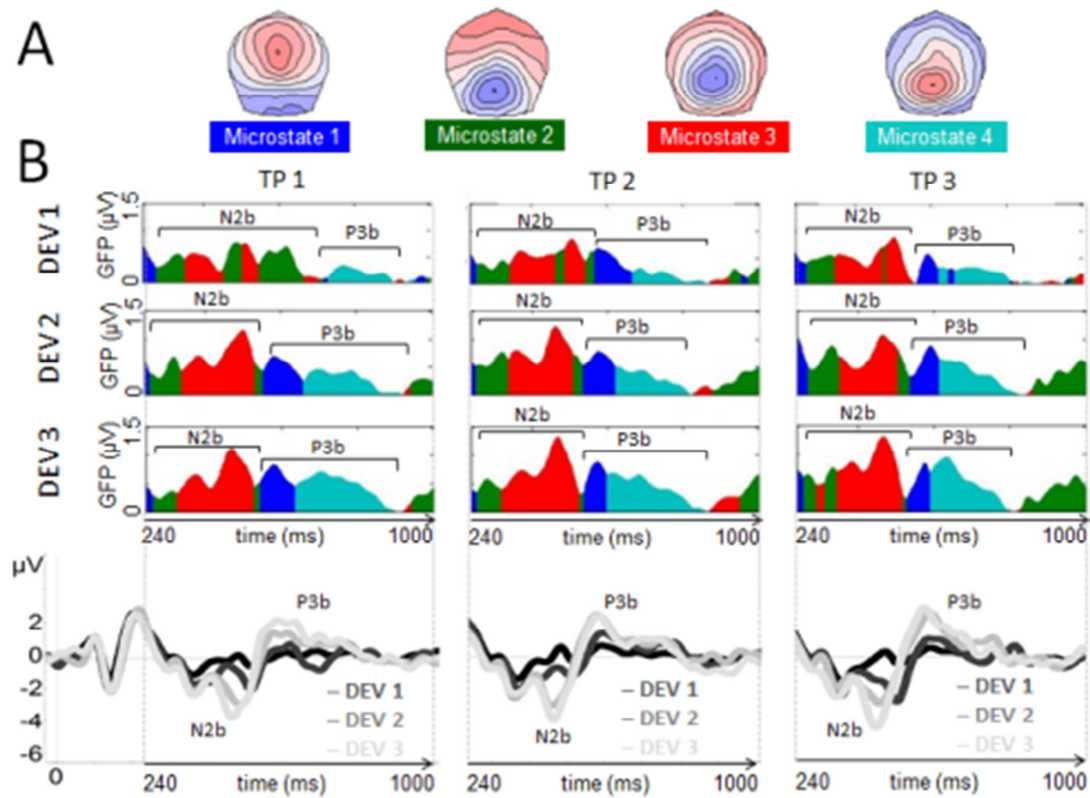


Figure 2: This graph shows the microstate analysis results for the easy stimulus block Ascha-Asa. **(A)** On the top of the figure, the four representative topographic maps are depicted: P3b-related Microstate 1 (in blue), N2b-related Microstate 2 (in green), N2b-related Microstate 3 (in red) and P3b-related Microstate 4 (in turquoise). **(B)** The time course of each microstate map depicted in (A) is shown here as a function of GFP (y-axis) for each DEV and each TP. Furthermore, the ERPs derived from electrode Cz are shown on the bottom of this figure.

In line with our hypotheses, we found that both, the N2b and the P3b had higher mean GFP and shorter onsets for stronger and therefore easier DEVs (see Table 1 and Figure 4A). The analysis further revealed longitudinal changes, but only in the cognitive-related microstates, and not in the perceptual-related microstates: Across TPs the onset of the P3b-like frontal positivity and the P3b-like posterior negativity shortened. However, we found interactions of DEV and TP in all microstate's onset and GFP, except for the onset of the N2b-like central negativity for which the interaction was not significant. The interactions revealed that the onsets decreased more strongly across TPs for the more difficult DEVs than for the easy DEVs. Moreover, the results showed that the longitudinal increase of the mean GFP was stronger for easier DEVs, although the main effects of TP were not significant for the mean GFP of any microstate investigated here.

Table 1: Descriptive results of microstate analysis for block 1 Ascha-Asa. Mean values are described separately for each microstate onset and mean GFP at each TP. Additionally, the p-values of the randomization statistics are described for the main effects TP and DEV, and the interactions of TP * DEV, separately for each microstate onset and mean GFP.

			TP 1	TP 2	TP 3	Main effect TP (p- value)	Main effect DEV (p- value)	Interaction TP * DEV (p- value)
Microstate 1: P3b-like frontal positivity	Onset (ms)	DEV 1	718	568	562	0.037 *	<0.001 ***	0.023 *
		DEV 2	556	536	538			
		DEV 3	544	538	530			
	GFP (μV)	DEV 1	0.358	0.535	0.404	0.369	<0.001 ***	<0.001 ***
		DEV 2	0.593	0.754	0.754			
		DEV 3	0.738	0.827	0.674			
Microstate 2: N2b-like posterior negativity	Onset (ms)	DEV 1	278	260	276	0.361	<0.001 ***	0.007 **
		DEV 2	256	254	270			
		DEV 3	262	258	260			
	GFP (μV)	DEV 1	0.582	0.505	0.567	0.128	<0.001 ***	<0.001 ***
		DEV 2	0.527	0.671	0.686			
		DEV 3	0.407	0.517	0.650			
Microstate 3: N2b-like central negativity	Onset (ms)	DEV 1	354	340	350	0.055	0.045 *	0.593
		DEV 2	340	340	354			
		DEV 3	324	322	294			
	GFP (μV)	DEV 1	0.564	0.639	0.572	0.537	<0.001 ***	<0.001 ***
		DEV 2	0.783	0.869	0.779			
		DEV 3	0.779	0.841	0.926			
Microstate 4: P3b-like posterior negativity	Onset (ms)	DEV 1	730	668	622	0.006 **	<0.001 ***	0.001***
		DEV 2	662	622	614			
		DEV 3	636	598	592			
	GFP (μV)	DEV 1	0.312	0.256	0.322	0.492	<0.001 ***	<0.001 ***
		DEV 2	0.416	0.388	0.465			
		DEV 3	0.624	0.519	0.636			

3.2. Results block 2: Ascha-Afa

3.2.1. Behavioral performance

The repeated-measure ANOVA for accuracy (see Figure 1) revealed a main effect of TP ($F(2,28)=7.83$, $p=0.002$, $\eta^2_p=0.36$), showing an increase of accuracy from TP 1 to TP 3 ($p=0.019$) (TP 1: $M=0.72$ $SD=0.02$, TP 2: $M=0.76$ $SD=0.02$, TP 3: $M=0.79$ $SD=0.02$). We also found a main effect of DEV ($F(1.06,14.81)=237.34$, $p<0.001$, $\eta^2_p=0.94$), revealing that the accuracy was higher for the easy DEV 3 compared to the difficult DEV 1 ($p<0.001$) and the moderately difficult DEV 2 ($p=0.017$). The moderately difficult DEV 2 was higher than difficult DEV 1 ($p<0.001$) (DEV 1: $M=0.32$ $SD=0.04$, DEV 2: $M=0.96$ $SD=0.01$, DEV 3: $M=0.99$ $SD=0.003$). The significant interaction between TP * DEV ($F(2.19,30.5.13)$, $p=0.01$, $\eta^2_p=0.27$) indicated that the increase of accuracy across the TPs was stronger for DEV 1 compared to DEV 2 and 3. For the RTs (see Figure 1), a main effect of TP was found ($F(1.41,16.90)=8.80$, $p=0.001$, $\eta^2_p=0.42$), showing a decrease of RTs from TP 1 to TP 2 ($p=0.046$) and to TP 3 ($p=0.019$) (TP 1: $M=828.28$ $SD=24.16$, TP 2: $M=781.49$ $SD=20.49$, TP 3: $M=765.32$ $SD=20.79$). There was also a main effect of DEV

($F(1.11,13.29)=137.57$, $p=0.001$, $\eta^2_p=0.92$) which revealed that the easy deviant DEV 3 had faster RTs than DEV 2 ($p<0.001$) and DEV 1 ($p<0.001$), and also that DEV 2 had faster RTs than DEV 1 ($p<0.001$) (DEV 1: $M=937.86$ $SD=28.14$, DEV 2: $M=741.01$ $SD=17.76$, DEV 3: $M=696.23$ $SD=18.01$). No interaction between DEV and TP was found.

3.2.2. Microstates

The accuracy for DEV 1 was low (32% on average across TPs), which resulted in a very small number of correct trials (<20 trials) to analyze. This paucity of trials did not allow for the reliable calculation of evoked potentials, which is the reasoning behind only including DEV 2 and DEV 3 in the following analysis. The microstate analysis of the DEV and TP within-subject factors again yielded four representative topographic scalp maps (see Figure 3A) that appear highly similar to the maps of stimulus Block 1. These occur in the same temporal order (see Figure 3B) in all conditions starting with the N2b-like posterior negativity at around 266 ms, and transitioning into the N2b-like central negativity that is intermitted by the more posterior negativity. Afterwards, there is a short period where the P3b-like frontal positivity is evoked and, following this, a longer interval where the P3b-like posterior positivity occurs (see Figure 4B). The map's onset and GFP were statistically tested for differences in DEV and TP by using a randomization statistic. Table 2 shows the descriptive data, as well as the p-values for the main effect of TP, DEV and the interaction of TP * DEV and Figure 4B depict the onset and GFP of each microstate as a function of TP and DEV.

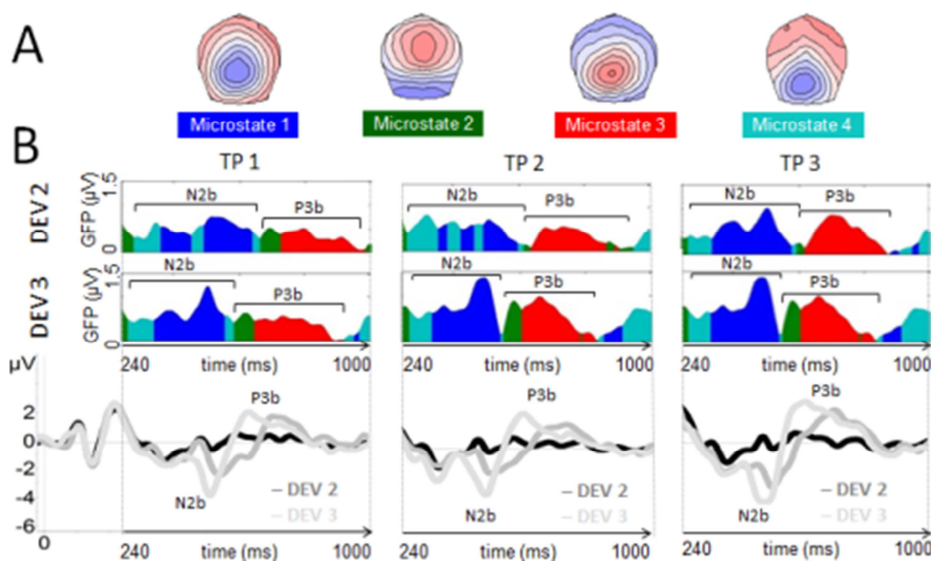


Figure 3: This graph shows the microstate analysis results for the easy stimulus block Ascha-Asa. **(A)** This figure shows the microstate analysis results for the difficult stimulus block Ascha-Afa. **(A)** This shows the

four representative topographic maps: N2b-related Microstate 1 (in blue), P3b-related Microstate 2 (in green), P3b-related Microstate 3 (in red) and N2b-related Microstate 4 (in turquoise). **(B)** The time course of each microstate map depicted in (A) is shown here as a function of GFP (y-axis) for each DEV and each TP. Furthermore, the ERPs derived from electrode Cz are shown on the bottom of this figure.

Similar to Block 1 and in line with our hypotheses, we found that all perceptual- and cognitive-related microstates had higher mean GFP and shorter onsets for easier DEVs (see Table 2 and Figure 4B). However, the onset of the N2b-like central microstate did not change as a function of DEV. Also the longitudinal results were similar to Block 1. In particular, we found that the onset decreased across TPs, but only for the two P3b-like microstates and not for the N2b-like microstates. This finding therefore supports our hypothesis that repeated auditory stimulation results in plasticity of auditory cognition. Furthermore, as in Block 1, we found several significant interactions of DEV and TP in the onset and GFP of all microstates, except in the onset of the two N2b-like microstates. The onsets of the two P3b-like microstates decreased more strongly for the more difficult DEVs than for the easy DEVs across TP. Furthermore, in all microstates, we found a stronger longitudinal increase of the mean GFP for the easier DEVs.

Table 2: Descriptive results of microstate analysis for block 2 Ascha-Afa. Mean values are described separately for each microstate onset and mean GFP at each TP. Additionally, the p-values of the randomization statistics are described for the main effects TP and DEV, and the interactions of TP * DEV, separately for each microstate onset and mean GFP.

			TP 1	TP 2	TP 3	Main effect TP (p- value)	Main effect DEV (p- value)	Interaction TP * DEV (p- value)
Microstate 1: N2b-like central negativity	Onset (ms)	DEV 2	362	358	338	0.395	0.769	0.952
		DEV 3	342	352	334			
	GFP (μ V)	DEV 2	0.612	0.569	0.687	0.448	<0.001 ***	<0.001 ***
		DEV 3	0.763	0.914	0.928			
Microstate 2: P3b-like frontal positivity	Onset (ms)	DEV 2	664	618	596	0.005 **	0.001 **	<0.001 ***
		DEV 3	586	558	550			
	GFP (μ V)	DEV 2	0.504	0.218	0.307	0.852	<0.001 ***	<0.001 ***
		DEV 3	0.631	0.703	0.745			
Microstate 3: P3b-like posterior negativity	Onset (ms)	DEV 2	726	638	620	0.003 **	0.001 **	0.001 **
		DEV 3	648	644	608			
	GFP (μ V)	DEV 2	0.395	0.445	0.579	0.077	<0.001 ***	0.008 **
		DEV 3	0.496	0.428	0.643			
Microstate 4: N2b-like posterior negativity	Onset (ms)	DEV 2	280	262	264	0.392	0.002 **	0.250
		DEV 3	262	260	266			
	GFP (μ V)	DEV 2	0.489	0.643	0.412	0.041*	<0.001***	0.010 *
		DEV 3	0.530	0.652	0.615			

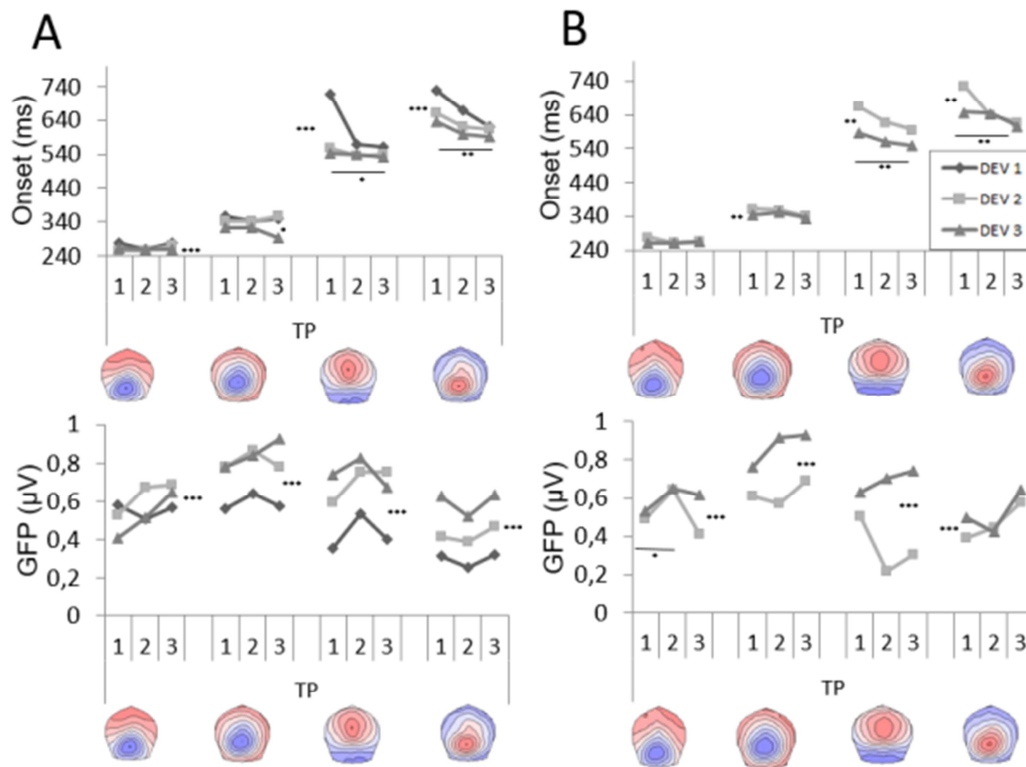


Figure 4: This graph shows the onsets and GFP of each microstate as a function of DEV and TP. **(A)** This part shows the results for the stimulus block Ascha-Asa. **(B)** depicts the results for the stimulus block Ascha-Afa. * depicts $p<0.05$, ** $p<0.01$ and *** $p<0.001$.

4. Discussion

4.1. Summary of findings

Several studies have described changes in amplitudes and latencies in early auditory evoked potentials (e.g., P50, N1, P2 and MMN) with longitudinal auditory learning (Bosnyak et al., 2004; Reinke et al., 2003; Ross et al., 2013; Sheehan et al., 2005; Tremblay et al., 1997, 2001, 2010, 2014a; Tremblay and Kraus, 2002). Surprisingly, changes in cognitive-related ERPs have not yet been studied as a function of repeated auditory stimulation, although it has recently been shown that auditory learning and cognition are closely related (Anderson et al., 2013a, 2013c, 2014). Taking this into consideration, a first innovative aspect of this work is that we obtained the time course of N2b/P3b AEP responses in a longitudinal design to study perceptual, but also cognitive-related modulations of auditory learning. Specifically, we used three TPs instead of two as in previous studies (Bosnyak et al., 2004; Reinke et al., 2003; Ross et al., 2013; Sheehan et al., 2005; Tremblay et al., 1997, 2001, 2010, 2014a; Tremblay and

Kraus, 2002), which revealed that the time course of behavior and neurophysiology was comparable as we found instant decreases in RT accompanied by decreases of onset in the P3b-related microstates at TP 2. Furthermore, another novelty of this study is that we applied an active oddball paradigm with multiple deviants to study the longitudinal cognitive-related plasticity as a function of perceptual difficulty. The results of this study underline the relevance of using multiple stimuli varying in their deviation strength, because we found interactions of DEV and TP for the GFP of most of the microstates, while the main effects of TP were not significant. This shows that the longitudinal time course of AEPs may vary tremendously depending on the deviant difficulty. Also, we used a data-driven analysis approach by using microstate analysis instead of traditional observer-biased electrode and latency picking. We consider this point as important, because our results revealed that both, the N2b and the P3b each had two latency peaks but at very different locations on the scalp at TP 1 leading to the two topographically distinct microstates for each, the N2b and the P3b. Thus, a single electrode or an electrode pool could not have detected this variation within the N2b and the P3b time course. Furthermore, also across the TPs, the electrode with the peak activation changed for specific time points in the AEP signal (see Figure 2B and 3B), a fact that could have tremendously bias the analyses using traditional AEP methods. Microstate analysis therefore essentially contributed to reveal topographical changes instead of single electrode modulations in the AEP time course and further segmented this signal into meaningful parts which were described by onset and mean GFP (Koenig et al., 2014; Michel et al., 2009b; Murray et al., 2008). In the following, we will briefly summarize the behavioral results and the data obtained by the microstate analysis and then integrate these findings into a broader context.

On a behavioral level, and in line with our predictions, we found that the detection of small spectral deviations resulted in a lower detection rate and longer RTs compared to salient spectral differences to the standard. Overall, our participants improved their detection rate across the four week test interval. However, only the improvement from TP 1 to TP 3 in the more difficult block (consisting of the high fricative /f/) reached significance, which seems to be the result of a ceiling effect. The detection rate for the easier block was already at 98% at TP1 across all deviants, which made an improvement at time point 2 and 3 highly unlikely. Nevertheless, our data also revealed that the detection of small spectral deviations improved more with repeated

exposure compared to more salient spectral deviations in the more difficult block, as expected. In addition, the RTs also systematically changed as a function of repeated exposure as shown by a decrease in RTs across the TPs. Unexpectedly, RTs were not sensitive to the DEV-specific increase in auditory performance. Our interpretation is that they may rather reflect an overall task facilitation. This reasoning can also be confirmed by the overall RT difference between the two blocks, showing that the mean RT across all DEVs was higher for the difficult block 2 (ascha-afa) compared to the easy block 1 (ascha-asa).

Regarding the neural level, both stimulus blocks evoked a similar time course of four similar microstate maps (Figure 2A and Figure 3A) at each TP, representing the incremental steps of perceptual and cognitive auditory processing. Interestingly, by using the microstate analysis, we detected two subprocesses of the N2b and the P3b: The processing of a deviant stimulus evokes a N2b-like posterior negativity first, then shifts into a N2b-like central negativity, which is followed by a P3b-like frontal positivity, and finally by a P3b-like posterior positivity. According to the literature, the N2b AEP component is a posteriorly distributed negativity (Ferdinand et al., 2015). In this work we found a change of the negativity peak from posterior to central within the N2b time interval at each TP and in both blocks. Nonetheless, as depicted in Figure 2B and 3B, the posterior and central N2b-like microstates interchange several times within the AEP time course suggesting only a very subtle and unstable difference between the two microstates. However, the temporal occurrence of a frontal P3b-like microstate first succeeded by a more parietal P3b-like microstate seems to be more stable across TP and conditions. Typically, a frontal positivity occurring around 300ms after deviation onset has been related to the P3a AEP component, which is elicited by nontargets in an active oddball paradigm (Katayama and Polich, 1998). The P3a component has been shown to induce attentional allocation to a surprising stimulus (Katayama and Polich, 1998). Our data suggests therefore that for a very brief moment, each deviant stimulus, although not new, may be processed as surprising as indicated by the occurrence of the frontal P3b-like positivity. After, the stimulus is labelled as a deviant and its memory trace updated (Debener et al., 2002; Kok, 1997; Polich, 2007; Volpe et al., 2007). The consistency in the temporal order of the topographical configurations between the two blocks indicates that well-tuned neural processes are evoked during spectral deviant detection. Moreover, these processes are evoked independent of stimulus material or

overall task difficulty. However, our microstate analysis revealed that the onset and the mean GFP of these processes change as a function of acoustic difficulty (DEV) and repeated exposure (TP) as will be discussed in the following sections.

4.2. Effect of spectral complexity on cognitive-related auditory processing

Both the N2b and the P3b were highly sensitive to spectral complexity as expected (Gaál et al., 2007; Johnson, 1986; Katayama and Polich, 1998; Kok, 1997): A stronger spectral deviation from the standard stimulus consistently resulted in higher accuracy and lower RT accompanied by higher mean GFP and shorter onset of all microstates investigated in this study. The exogenous-driven N2b component is evoked by the detection of unexpected stimuli that are task-relevant in a stream of standard stimuli (Breton et al., 1988; Ferdinand et al., 2008, 2015; Näätänen et al., 1982). In comparison, the MMN, also belonging to the N2 AEP family, is elicited by unexpected stimuli that are task-irrelevant (Ferdinand et al., 2008, 2015) and therefore reflects a sensory-driven process. The N2b on the other hand is thought to reflect a stimulus categorization process (Näätänen and Gaillard, 1983; Simson et al., 1977), and as such indicates that when an unexpected stimulus violates our (stimulus) expectation, an expectation update regarding the upcoming stimuli is needed (Ferdinand et al., 2008, 2015). This suggests that the N2b is evoked by stimuli that contribute to learning (Ferdinand et al., 2008, 2015). In line with previous work, a strong deviation from the standard stimulus resulted in faster, more intense and synchronous neural categorization of the deviant stimulus (Ferdinand et al., 2008, 2015; Novitski et al., 2004; Rogenmoser et al., 2014; Rüsseler et al., 2003). This, in turn, allowed the subject to learn faster and more accurately that the stimulus was different from the standard and therefore a target, which was reflected in the higher accuracy and the shorter RT while detecting the strong deviant stimulus. The following neural process, as reflected by the P3b, is also only evoked by target stimuli (Squires et al., 1975). Although there is a myriad of publications on the P300 and its subcomponents, its interpretations in the literature are somewhat unspecific and varied. Nevertheless, it has been described as reflecting later and higher-order processes such as stimulus evaluation, updating of working memory after unexpected events, and cognitive resources in general (Donchin and Coles, 1988; Johnson, 1986; Kok, 1997; Polich, 2004, 2007; van Dinteren et al., 2014). Studies have shown that the P3b is also responsive to the degree of target deviation (Berti et al., 2004; Falkenstein et al., 1994; Katayama and Polich, 1998), which

is in line with our results showing shorter latencies and higher mean GFP with stronger spectral deviation. More salient acoustic differences to the standard therefore resulted in a faster, stronger and more synchronous activation of memory updating processes, evoked by a wide-range network of bilateral frontal, parietal, limbic, cingulate and temporo-occipital sources (Volpe et al., 2007), and supported by the norepinephrine system (Nieuwenhuis et al., 2005). In sum, we therefore interpret that spectral deviation is first perceptually detected as reflected in the N2b, then capturing attention as reflected in frontal P3b (see elaborations above) and finally the memory is updated by storing the stimulus labelled as a target as reflected in the parietal P3b component.

4.3. Cognitive-related auditory learning

Interestingly, the onset systematically shortened across TPs, but only for the cognitive-related P3b-like maps, and not for the perceptual N2b-like maps. As expected, the shortening of onsets across TPs was stronger for difficult DEVs compared to easier DEVs, even though, again, this finding only applied to the P3b-like maps (see Figure 4). Thus, the systematic modulations of the microstate onsets are indicative of cognitive-related auditory plasticity, occurring with repeated auditory stimulation after two weeks. These neural changes that evolved between the measurement time points may be subjected to consolidation processes where all relevant information is stored in long-term memory (Atienza et al., 2002; Karni and Sagi, 1993). Our results therefore show specificity on such modulations of cognitive processes underlying longitudinal auditory learning. However, we could not find any changes across TP in the mean GFP of the N2b-like and the P3b-like microstates. As for the interactions of mean GFP (see Figure 4), overall we found a stronger increase of mean GFP across the four weeks in spectrally strong DEVs compared to weak DEVs.

These results suggest that attentional relocation and memory updating following the processing of a deviant stimulus were executed faster with repeated exposure after two weeks. More specifically, spectrally complex stimuli were more subjected to cognitive-related auditory plasticity, as was shown by stronger P3b-related microstate onset reduction compared to salient stimuli. Not in line with this finding, previous studies investigating N1/P2 ERPs as biomarkers for auditory learning reported amplitude changes rather than latency changes with repeated exposure (Bosnyak et al., 2004; Brattico et al., 2003; Menning et al., 2000; Tremblay et al., 2014a; Wagner et al.,

2013). Remarkably, another study which also used an active paradigm consisting of a vowel identification task, found latency effects with repeated measurements (Reinke et al., 2003). In order to clarify these findings, future studies should test the idea that latencies may be mainly subjected to auditory plasticity when task-relevant stimuli and therefore attentional processes or memory functions are involved (Tremblay et al., 2014a). A study design similar to the one presented here, but also including non-target deviant stimuli, would be preferred to test this hypothesis. The latency shifts that we described in our study also pointed to the fact that, after cognitive-related auditory learning at TP 3, the microstate onset differences evoked by the difficult and easy stimuli were much lower compared to TP 1. Therefore, the more difficult stimuli evoked the memory updating process at TP 3 just as fast as the easy stimuli did at TP 1, which underlines our interpretation of microstate-onset-related plasticity. Moreover, this interpretation is supported by the behavioral data showing a reduction in behavioral reaction times as a function of repeated stimulus exposure.

Interestingly, for the GFP we found an effect in another direction: Cognitive-related auditory learning resulted in more distinct processing of the differently complex stimulus material. More specifically, the GFP of N2b- and P3b-related microstates evoked by stimuli varying in their complexity was quite similar at TP 1, but more distinct at TP 3. This was mainly a result of stronger GFP increases for the more salient stimuli compared to the difficult stimuli with only small spectral deviations to the standard. With discrimination learning, therefore, the neural representation of stimuli becomes more distinct, or, as has been shown by a previous fMRI study (Guenther et al., 2004), it increases in size. Moreover, these neural patterns were supported by some (small) increases in the discrimination ability between standard and deviant stimuli. These behavioral increases, however, were only found in the more difficult stimulus block, and only between TP 1 and TP 3. These results therefore imply that the neural modulations of the N2b- and the P3b-related microstates are more strongly related to differences in the neural representation of syllables rather than the behavioral outcome, a finding which has also been described for the P2 (Tremblay et al., 2014a). In future studies, the relation between behavioral auditory learning and N2b- and P3b-related changes should be studied in more difficult situations, in which participants have a better chance to increase their performance. Collectively, the authors think that the onset and the GFP of cognitive-related ERPs are suitable markers to study cognitive-

related auditory learning, as they were both systematically subjected to longitudinal plasticity. Furthermore, the stronger neural changes from TP 1 to TP 2 compared to TP 2 to TP 3 also suggest that the cognitive-related auditory system reacts instantly (in this study, after two weeks) to repeated exposure and then stabilizes afterwards.

4.4. Outlook

Researchers have started to think of auditory perception as being an interaction of peripheral, central and cognitive contributors (Humes et al., 2012), especially in older adults. Our results support this line of reasoning, as they indicate that cognitive factors such as attention and memory processes are highly relevant for auditory learning, as reflected in the P3b changes that occurred during the two and four weeks retest interval. Furthermore, these results have implications for auditory training studies. Recent auditory training studies focused mainly on training of and transfer effects to sensory processes in the brainstem or in early cortical evoked potentials (Bosnyak et al., 2004; Reinke et al., 2003; Ross et al., 2013; Sheehan et al., 2005; Tremblay et al., 1997, 2001, 2010, 2014a; Tremblay and Kraus, 2002). Due to the fact that the current study described changes in attentional and memory processes as a function of auditory learning, future studies should use auditory cognition as measured by the P3b as an outcome variable. In the emerging field of Cognitive Hearing Science (Arlinger et al., 2009), the role of cognition during speech processing is being investigated. One relevant area of application is research on the benefits of high cognitive capacities in the context of hearing loss in older adults and hearing aid use. However, longitudinal studies in this field are scarce and have not always taken into account neurophysiological markers on the course of sensory-driven and cognitive-related auditory learning. The authors are of the opinion that the present paradigm is highly suitable to study the relations between perceptual and cognitive mechanisms during auditory learning. For instance, it could be specifically interesting because many hearing impaired older adults often complain about getting tired fast because auditory processing needs too much cognitive effort (McCoy et al., 2005; Stewart and Wingfield, 2009). Thus, the GFP of the P3b may be a suitable marker for auditory-related cognitive effort in such a sample. Additionally, this study showed perceptual increases in spectrally manipulated speech in high-pitched fricatives, which, among other parameters, has been shown to decline very rapidly in older adults (see Humes et al., 2012 for an overview).

2.3. Study III: The Impact of Hearing Aids and Hearing Loss on Auditory Plasticity Across Three Months – An Electrical Neuroimaging Study

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A similar version of this manuscript has been submitted for publication to *Hearing Research*

Abstract

The present study investigates behavioral and electrophysiological auditory and cognitive-related plasticity in healthy older adults (60-77 years), who were divided into three groups: Group 1 was moderately hearing-impaired, experienced hearing aid users, and fitted with new hearing aids using non-linear frequency compression (NLFC on); Group 2 used the same type of hearing aids but NLFC was switched off (NLFC off); Group 3 represented normal-for-age hearing individuals (NHO) as controls matched for IQ, sex, gender and age. At five measurement time points (M1-M5) across three months, a series of active oddball tasks were administered, while EEG was recorded. The stimuli comprised syllables consisting of natural high-pitched fricatives (/sh/, /s/, and /f/), these being typically problematic for individuals with presbycusis. By applying a data-driven microstate approach to obtain global field power (GFP) as a measure of processing effort, the modulations of perceptual (P50, N1, P2) and cognitive-related (N2b, P3b) auditory evoked potentials were calculated and attributed to behavioral changes (accuracy and reaction time) across time.

All groups improved their performance across time, but NHO showed consistently higher accuracy and faster reaction times than the hearing-impaired

groups, especially under difficult conditions. Electrophysiological results complemented this finding by demonstrating longer latencies in the P50 and the N1 peak in hearing aid users. Furthermore, the GFP of cognitive-related evoked potentials decreased from M1 to M2 in the NHO group, while this decrease was only evident in the hearing-impaired groups at M5. Only after twelve weeks of hearing aid use of eight hours each day, we found a significant lower GFP in the P3b of the group with NLFC on as compared to the group with NLFC off.

These findings suggest higher processing effort, as evidenced by higher GFP, in hearing-impaired individuals when compared to those with normal hearing, although the hearing-impaired show a decrease of processing effort after repeated stimulus exposure. In addition, we were able to show that the acclimatization to a new hearing aid algorithm may take several weeks.

1. Introduction

Peripheral age-related hearing loss (presbycusis), caused by a damage to the cochlea or the auditory nerve (Chertoff and Jacobsen, 2012), challenges the central auditory system with delivering a disrupted acoustic signal to the cortex. Hearing aids (HA), the most common treatments for presbycusis, have been developed to partially restore the signal by amplifying sounds in order to improve audibility and also by applying noise reduction algorithms to support intelligibility. Although improvement in speech intelligibility has been shown in aided compared to unaided listening conditions (Coez et al., 2010), the question if and how central auditory processing changes as a function of HAs remains unclear.

Up to date, only a handful of studies examined early auditory evoked potentials (AEP) such as the P50, the N1, and the P2 while fit young, normal-hearing listeners with hearing aids for the first time. Comparing the aided to the unaided listening conditions, some studies reported increases in the peak amplitude of AEPs (Miller and Zhang, 2014; Tremblay et al., 2006a), while others reported a decrease of amplitudes (Billings et al., 2011), delayed latencies (Marynewich et al., 2012; Miller and Zhang, 2014), or no significant differences (Billings et al., 2007; Marynewich et al., 2012). Thus, these results remain somewhat difficult to interpret for two reasons. First, these studies applied passive paradigms which do not allow relating the neurophysiological data to behavior, which would have resulted in less ambiguous interpretations of the decreases and increases in amplitudes and latencies. Second, it remains unclear to what extent these results apply to older adults, who are typically suffering from presbycusis.

Nevertheless, two feasibility studies showed that the acoustic change complex (ACC) (Tremblay et al., 2006b) and the speech-evoked envelope following response (EFR) (Easwar et al., 2015) can be reliably recorded in older hearing aid users. The ACC and the EFR can be measured with scalp EEG, with the ACC being a cortical auditory evoked potential elicited in response to an acoustic change (Kim, 2015) and the EFR being a phase locked response to the stimulus envelope frequency (Picton et al., 2003). Furthermore, one other study reported an increase of the P2 amplitude in response to passively presented lower tones and a P2 amplitude decrease in response to passively

presented higher tones for aided compared to unaided listening in older adults with age-related hearing loss (Bertoli et al., 2011).

In this paper, we therefore used an active oddball paradigm to assess accuracy and reaction time of oddball detection and to compare latencies and global field power (GFP), here used as a correlate for processing effort (Lemke and Besser, 2016), of early perceptual AEPs (P50, N1, P2), but also later cognitive-related AEPs (N2b, P3b) in older adults with moderate presbycusis who are experienced hearing aid users to an age matched control group without hearing loss. Investigating the longitudinal modulations of cognitive-related AEPs is crucial, as several behavioral studies have found facilitating effects of hearing aids on cognitive-related auditory processes (Doherty and Desjardins, 2015; Lavie et al., 2015). In addition, we followed the two groups for three months (measurement time points M1-M5) in order to study central auditory plasticity as a function of the HA time of usage. Longitudinal research to investigate within-group changes across time is much needed in this field, but still rare. Moreover, the hearing-impaired group was further divided into two subgroups, one which was provided with traditional amplification hearing aids, while the other was equipped with a specific hearing aid feature, namely nonlinear frequency compression (NLFC).

NLFC is a common hearing aid feature, in which the high-frequency signal, typically no longer accessible to the older hearing-impaired, is compressed into a lower frequency range. It only compresses the signal above a certain threshold, which is determined individually (McDermott and Henshall, 2010). NLFC does not compress lower frequencies in order to avoid artifacts in vowels and it has been reported to improve the recognition of high-frequency consonants, such as fricatives and monosyllabic words (Alexander, 2016; McCreery et al., 2014; Wolfe et al., 2010, 2011, 2015), although not all study participants benefit from NLFC to the same extent (Bohnert et al., 2010; Ching et al., 2013; Hillock-Dunn et al., 2014; Simpson et al., 2005, 2006).

At M1, we predicted longer latencies in P50, N1, and P2 in hearing aid users compared to those with normal-for-age hearing as has been shown in within-subject designs in younger adults (Korczak et al., 2005; Marynewich et al., 2012; Miller and Zhang, 2014) and in studies comparing CI users to those with normal hearing (Finke et

al., 2016). Further, for all groups, we assumed to find increases of oddball detection accuracy, decreases of reaction time and decreases in AEP latencies across the measurement time points as was shown in a similar experiment with younger adults (Giroud et al., 2017). Importantly, we also expected to find group * M interactions from M2 to M3 revealing stronger increases of accuracy and stronger decreases of reaction time and AEP latencies for normal-hearing participants as compared to hearing impaired, because the central auditory system of hearing aid users is supposed to adapt to hearing aid use for several weeks in order to process the auditory stimulus material appropriately which is altered due to the hearing aid (Wolfe et al., 2011, 2015). We further predicted that the group with NLFC on will show stronger increases in detection accuracy and decreases in reaction time and AEP latencies compared to the group with pure amplification (Alexander, 2016; Wolfe et al., 2011, 2015), which will be tested in a group * M interaction. Moreover, we expected that usage of NLFC will lead to stronger decrease of processing effort, measured by the GFP of the N2b and P3b, when compared to the group without NLFC (Hällgren et al., 2005; Hornsby, 2013; Rudner, 2016; Tremblay and Backer, 2016)

2. Materials and Methods

2.1. Participants

Thirty older adults with moderate age-related hearing loss were recruited through local audiologists. They were all experienced hearing aid users for at least one year, but had no experience with NLFC as used in SoundRecover. At the start of the study each participant received two new binaural hearing aids, model Phonak Ambra M H20, which were fitted to their individual audiograms by a licensed audiologist during three sessions, each separated by an interval of one week. Twenty-four participants used custom-made SlimTips due to small hearing canals or non-acceptation, and six used standard domes. The vent was determined using the Phonak designed technology AOV (acoustically optimized vent) to ensure the right-sized vent for each custom-made SlimTip. The hearing-impaired participants were divided randomly into two groups: Group 1 with NLFC (SoundRecover) turned on after the first measurement time point (N = 13, age range 64 to 77 years, mean age = 70.31, SD = 5.19, one female, mean IQ = 106.31, SD = 9.82, two left-handed), and Group 2 with NLFC turned off (N = 13, age

range 61 to 77 years, mean age = 70.38, SD = 4.27, four females, mean IQ = 105.23, SD = 17.73, two left-handed). Age and mean IQ were not different between the two groups (age: $t(24) = -.04, p = .97$, IQ: $t(24) = .19, p = .85$). Intelligence was measured using the KAI test (Kurztest für die Basisgrösse allgemeiner Intelligenz (Lehrl, 1992). Three participants had to be excluded from further analyses because of dropout from the study during the longitudinal assessment and one because of EEG artifacts (eye blinks every second).

At each measurement time point, we also assessed how many hours on average per day the participants had been wearing their hearing aids since the last measurement time point by analyzing the hearing aid logfiles. We could not find any differences between the two hearing aid groups in the average usage hours (M2: $t(23) = .86, p = .40$, M3: $t(24) = .75, p = .46$, M4: $t(23) = 1.35, p = .19$, M5: $t(24) = .94, p = .36$).

In addition, a control group of older adults with normal-for-age hearing (NHO) was recruited ($N = 13$, age range 62 to 76, mean age = 69.23, SD = 3.94, 5 females, mean IQ = 102.92, SD = 17.55). Age and IQ were not different between NHO and the hearing-impaired (HI) groups (age: $t(37) = .74, p = .46$, IQ: $t(37) = .55, p = .59$). All participants but four were right-handed, as indicated by standard handedness questionnaires (Annett, 1970b; Bryden, 1977). All participants were native German or Swiss German speakers. They reported no history of present or past neurological, psychiatric, or neuropsychological disorders. In addition, they all denied the consumption of drugs, illegal medication, and the continuous use of blood-thinners. None of the participants suffered from chronic tinnitus.

The local ethics committee of the Canton Zurich approved the study, and written informed consent was obtained from all participants. Participants were paid for their participation.

2.2. Hearing

The two moderately hearing-impaired groups (NLFC on and NLFC off) were tested regarding their pure-tone thresholds by a hearing care professional (see Figure 1). They were tested using an Aurical Plus audiometer (GN otometrics) with headphones (Telephonics TDH39), whereas the NHO group underwent testing with the Maico ST20

Audiometers (Maico Diagnostic GmbH, Berlin, Germany: <http://www.maico-diagnostic.com/>). Only hearing-impaired individuals who met the fitting range of the Phonak Ambra M H2O (between 15-75 dB hearing loss at 125 to 500 Hz, and between 25-90 dB hearing loss at 750-8000 Hz) were included in the study. All included participants exhibited a similar bilateral hearing acuity for the average of 0.5, 1, 2, 3, 4, 6, and 8 kHz (max. difference left and right ear < 15 dB HL). In addition, for the NHO participant group neither ear exceeded the threshold of > 30 dB HL for 0.5, 1, 2, 3, and 4 kHz. Furthermore, the required thresholds for 6 kHz tones were < 50 dB HL and for 8 kHz tones < 60 dB HL. The online hearing test Med-el, which is available at <http://www.medel.com/de/online-hoertest/>, was administered to the NHO group using the German version (Zokoll et al., 2012). This is an online digit triplet test that presents digit triplets in noise (Buschermöhle et al., 2014, 2015). Participants were required to recall three monosyllabic digits after having heard them presented through noise via headphones. The volume of the triplets varied adaptively in order to find the 50% intelligibility threshold of the triplets. All tested participants were excluded from taking part in the study when they had a higher signal-to-noise ratio (SNR) than 2.9 dB, however all tested participants passed. This test was developed as part of the European HearCom project (Vlaming et al., 2011).

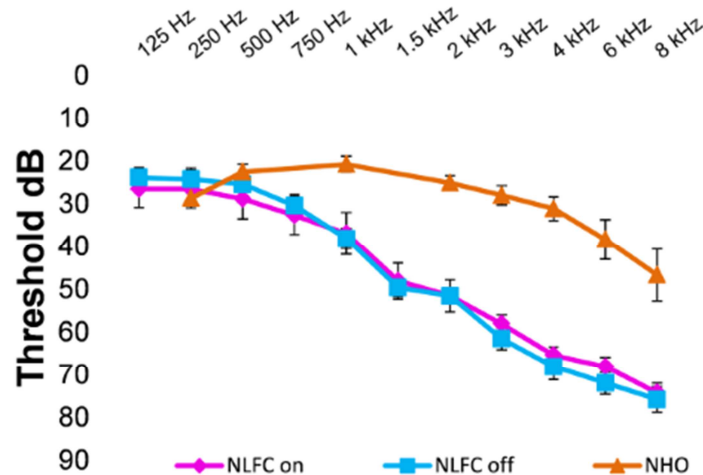


Figure 1: Audiogram of the normal hearing older group (NHO), the moderately hearing impaired group using NLFC (NLFC on) and the moderately hearing impaired group having NLFC turned off in their hearing aid (NLFC off).

2.3. Stimuli

The logatomes *asa* (/ʼa:sa/), *ascha* (/ʼa:ʃa/), and *afa* (/ʼa:fa/) from the phoneme perception test (Boretzki et al., 2011; Schmitt et al., 2015) were used in our study. This stimulus material had already been used in a previous study using EEG (Giroud et al., 2017). The alveolar /s/, the post-alveolar /sch/ and the labiodental /f/ were embedded in an initial and a final /a/ sound. The center frequency of the /s/ was 7.65 kHz, of the /ʃ/ was 3.14 kHz, and of the /f/ was 11.03 kHz. These high-pitched fricatives were chosen because the NLFC algorithm specifically targets the rehabilitation of hearing in a high pitch range that is typically lost in adults with moderate age-related hearing loss. In order to create two equidistant intermediate acoustic stimuli between the two logatomes ‘ascha’ and ‘asa’, ‘afa’ and ‘asa’, and ‘ascha’ and ‘afa’ (see Figure 2), they were morphed (Zorn, 2000) in their aspects of pitch, energy, spectrum, and rhythm. Each of the three stimulus combinations were tested in a separate block (see experimental procedure). Block 1 contained the stimulus material with the stimulus pair *ascha* (/ʼa:ʃa/) and *asa* (/ʼa:sa/) and its two morphings, whereas in block 2 the logatomes were replaced by *ascha* (/ʼa:ʃa/) and *afa* (/ʼa:fa/), and in block 3 by *afa* (/ʼa:fa/) and *asa* (/ʼa:sa/). The first stimulus of each stimulus pair was used as the standard, while the second original stimulus and the two morphed stimuli served as deviants of different difficulty. The morphed stimulus with the weaker acoustic deviation from the standard was called Deviant 1 (DEV 1). The morphed stimulus with the stronger acoustic deviation from the standard was called Deviant 2 (DEV 2). The second original stimulus of each stimulus pair was used as Deviant 3 (DEV 3) and had the strongest acoustic distance from the standard stimulus (see Figure 3).



Figure 2: The combination of the stimulus material for the three different stimulus blocks. Embedded between an initial and a final /a/ sound were the alveolar /s/, the post-alveolar /sch/ and the labiodental /f/. Two equidistant intermediate acoustic stimuli between the two logatomes ‘ascha’ and ‘asa’, ‘afa’ and ‘asa’, and ‘ascha’ and ‘afa’ were created by morphing (Zorn, 2000) in their aspects of pitch, energy, spectrum, and rhythm.

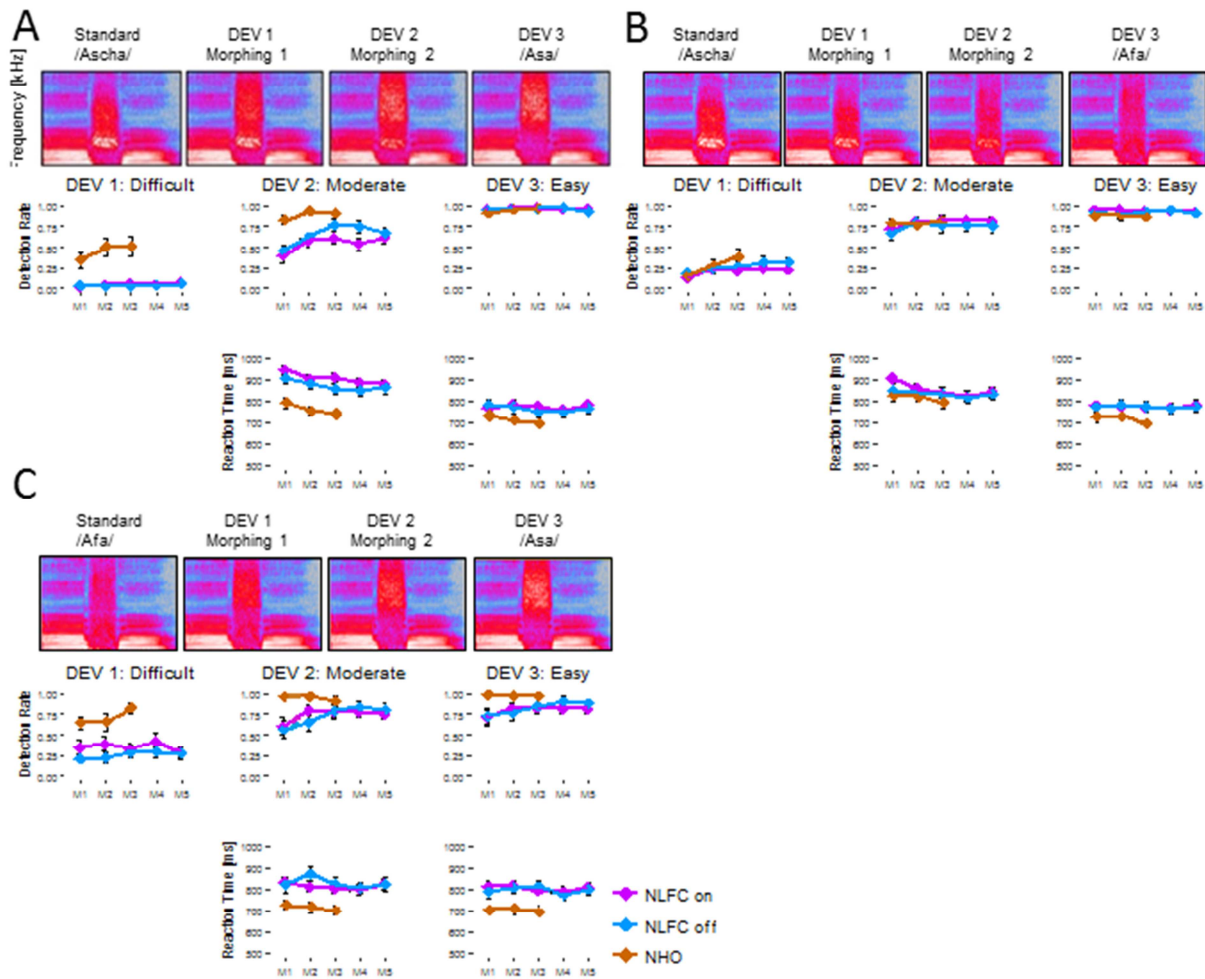


Figure 2: This Figure depicts the spectrogram of the stimulus material (top row), and the behavioral data, namely the deviant detection rate (middle row) and the reaction times (lowest row) for each stimulus and for each measurement time point (M1, M2, M3, M4, and M5). A) depicts the results for the stimulus block 1 with /Ascha/ as a standard stimulus, and /Asa/ as the easy deviant DEV 3 with DEV 1 and DEV 2 two equidistant morphings between standard stimulus and DEV 3. B) shows stimulus block 2 with the standard stimulus /Ascha/ and DEV 3 /Afa/ together with the two morphings. C) shows stimulus block 3 with the standard stimulus /Afa/ and the easy deviant DEV 3 /Asa/, while DEV 1 and DEV 2 are equidistant morphings between standard stimulus and DEV 3.

2.4. Longitudinal design

The two hearing-impaired groups had five sessions (M1-M5) during which EEG was measured. The NHO group attended the first three appointments. The participants were invited for the first recording time point (M1), after which NLFC was turned on in the NLFC on group, and were then retested two weeks (M2), four weeks (M3), six weeks

(M4) and at a follow up of 12 weeks (M5) after M1 (see Figure 2). Each participant's follow-up appointments were scheduled at the day of the week and the same time of day as their initial appointment to control for changes in attention during the day. Only one participant of the hearing-impaired group had to be re-scheduled at M3 and was tested one day later than usual and one other participant of the NHO group was re-scheduled at M2 and was tested two days later than usual.

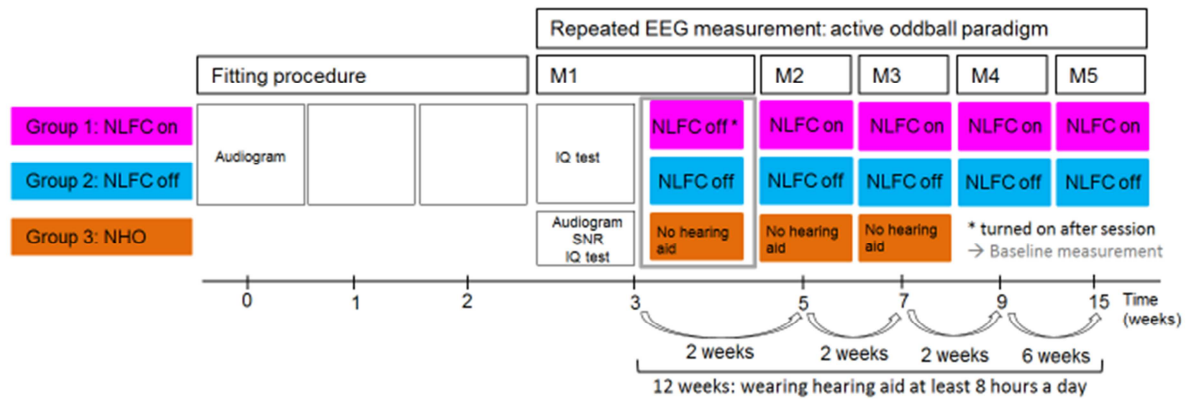


Figure 4 depicts an overview of the study design. The three participant groups are colored with pink (Group1: NLFC turned on), blue (Group 2: NLFC turned off), and gold (Group 3: normal-hearing older, NHO). Within three meetings, the hearing aids were individually fitted for the two hearing-impaired groups (Group 1 and Group 2) according to their audiograms as assessed in the first meeting. After three weeks, the measurement time point 1 (M1) was administered, where the IQ, the audiogram for Group 3 was assessed. Furthermore, the active oddball paradigm with the three different stimulus blocks was scheduled, while EEG was recorded. The normal-hearing group (Group 3) was tested without hearing aids, while the two moderately hearing-impaired groups (Group 1 and Group 2) were tested with their hearing aids, but in both groups NLFC was turned off for the testing, which allowed to use this session as a baseline measurement. After the session, NLFC was turned on, only in Group 1. From this day, the hearing-impaired groups (in Group 1 with NLFC on and in Group 2 with NLFC off) were instructed to wear their hearing aids for at least eight hours each day, until the end of the study after three months and also during each testing at the following measurement time points. Measurement time point 2 (M2), 3 (M3), and 4 (M4) were administered at a two weeks interval, while measurement time point 5 (M5) was scheduled six weeks after measurement time point 4 (M4). During M2, M3, M4, and M5 participants took part only in the EEG testing with the active oddball task.

2.5. Experimental procedure

The experimental procedure had been established in a previous study (Giroud et al., 2017). During each measurement time point, participants were seated in a

comfortable chair at a distance of about 75 cm in front of a speaker which was placed in front of a screen. Using a speaker instead of headphones was more applicable for hearing aid users. The speaker (KEF, HTS2001.2, 8 Ω) with the Uni-Q array technology was used to provide a single source of sound with a frequency range of 80 Hz – 27 kHz and a maximum output of 104 dB SPL. Before starting the EEG recording, the volume of a white noise sound was manually set to 65 dB using an audiometer (AL1 Acoustilyzer).

To avoid eye movement artifacts during EEG measurements, participants were instructed to fixate on the cross presented on the screen. Participants performed two runs of each of the three blocks, each lasting about nine minutes and followed by a short pause. Their order was randomized between participants and between measurement time points. The standard stimulus was presented 540 times ($p=0.75$) during each block, while each deviant was presented 60 times ($p=0.083$) in a randomized order with an inter-stimulus interval of 730 ms. The Presentation software (www.neurobs.com; version 14.5) controlled the experiment. The task for participants was to listen to the stream of stimuli and to press the mouse button with the right index finger when a deviant stimulus was identified. Correct trials were averaged, resulting in a maximum of 60 trials per deviant and 540 trials for the standard stimulus. Before each EEG recording, participants were asked to set the volume level of the three original stimuli to an equal loudness level in 1 dB steps. If the volume was perceived differently by the participants, a jitter in volume for the standard stimulus was introduced: A jitter of 1 dB if the difference between the two stimuli was set to 1 dB, or a jitter of 2 dB if the difference between the two stimuli was set to 2 dB or more. The maximum perceived level difference between the stimuli was 2 dB. All stimuli were presented at a standardized volume of 65 dB SPL, except that the standard stimulus volume was jittered as described above. This procedure allowed participants to detect a deviant only by its perceived qualitative difference to the standard rather than by its perceived difference in loudness.

2.6. EEG recordings and preprocessing

By using the high-density Geodesic EEG system (Electrical Geodesics, Inc., USA) with 256 scalp electrodes, EEG was continuously recorded during each measurement time point. Impedances for all electrodes were kept below 30 k Ω . The data was online band-pass filtered between 0.1-100 Hz, while Cz served as the online reference. Offline,

the data was re-referenced to linked mastoids for visual inspection of the grand averages at electrode Cz, and afterwards to average references for further data analyses. The data was digitized at a sampling rate of 500 Hz. For the preprocessing steps, Brain Vision Analyzer Software (Version 2.0.4, Brainproducts, Munich, Germany) was used. First, the electrodes placed on the cheeks and on the neck were removed reducing the number of electrodes from 256 to 204. Second, the data was filtered offline between 0.1-20 Hz (24 dB/oct). An independent component analysis (ICA) was used to remove eye movements and eye blinks (Jung et al., 2000). Noisy channels were interpolated using topographic interpolation (Perrin et al., 1987) and amplitude changes higher than 100 μ V were removed with a semi-automatic raw data inspection. After the data was clean, it was segmented into 1300 ms segments (from 100 ms pre-stimulus to 1200 ms post-stimulus) and baseline corrected relative to the 100 to 0 ms pre-stimulus time period. Only correct trials (when the deviant was successfully detected) were subjected to further EEG analyses. The hearing-impaired participants only detected sufficiently enough deviant stimuli in stimulus block 1 with the stimuli Ascha-Asa: Each participant with hearing impairment was able to identify at least 30 weak deviants (DEV 3) at each measurement time point, which allowed for the reliable calculation of the evoked activity (>30 correct trials for all measurement time points for each participant). In fact, for DEV 3 of the stimulus block Ascha-Asa, we were able to analyze on average 56.37 correct trials (min=30, max=60) at M1. We note here that for the following EEG analyses, we therefore focused only on the weak DEV 3 of the stimulus block Ascha-Asa, because not every hearing-impaired participant's performance was sufficiently accurate (<30 correct) DEV 1 and DEV 2 at M1 (Ascha-Asa DEV 1 min=0, max=9; Ascha-Asa DEV 2 min=2, max=56). These trials were averaged to compute the event-related potentials (ERPs), separately for each deviant and each measurement time point.

2.7. Microstates

The use of a topographical approach has several advantages when compared to classical one-electrode or one-electrode-pool analyses: First, single electrodes do not have to be manually chosen. Second, topographical measures are reference independent (Koenig et al., 2014; Lehmann and Skrandies, 1980, 1984). Third, topographical dissimilarities between conditions or groups can be interpreted directly, as they reflect differences in the configuration of the underlying neural networks (Murray et al., 2008;

Vaughan, 1982). Fourth, the use of a temporal filter when applying the microstate approach (Koenig et al., 2014; Murray et al., 2008) allows for the identification of temporally stable topographical configurations, which can then be analyzed in a data-driven manner, and forgoing the need to define arbitrary time windows of interest in an ERP time course a priori (Giroud et al., 2017; Kühnis et al., 2013b; Michel et al., 2009a; Murray et al., 2008; Pascual-Marqui et al., 1995). Microstates can be compared statistically between groups and conditions using for example their mean GFP and the latency of the peak. We used the hierarchical clustering algorithm AAHC (atomize and agglomerate hierarchical clustering) from the software Cartool (Version3.55, The Cartool community group, retrieved from <https://sites.google.com/site/cartoolcommunity/>) to identify the stable topographies across all grand averaged data (Brunet et al., 2011; Murray et al., 2008). To this end, we calculated the difference waves. Each data point of the grand averaged difference waves - separately from the five measurement time points for the two hearing-impaired groups and the three measurement time points for the NHO group - was treated as one cluster. Some clusters were then randomly selected and spatially correlated to the remaining clusters of the data set. Each template usually yields the highest correlation coefficient for several consecutive time points, and we specified that all unstable maps shorter than 20 ms were to be rejected. We then averaged all clusters that reached the highest spatial correlation at a specific time interval. The resulting averaged cluster formed the new template map for that group. Within each group, the clusters with the lowest global explained variance (GEV) were then identified and reassigned to the clusters with the highest correlation to the new map. In order to identify the optimal number of clusters for this step, we applied the Krzanowski-Lai (KL) criteria (Krzanowski and Lai, 1988; Murray et al., 2008). For fitting the clusters back to the individual data, we calculated the spatial correlation of the clusters with the individual subject data (Brunet et al., 2011; Murray et al., 2008). As dependent parameters we then obtained the mean GFP and the latency of the peak GFP of all microstates. With the obtained parameters we then computed a one-way ANOVA for the obtained microstate parameters to check for baseline differences at M1 between groups, at which both hearing-impaired groups had NLFC off. After, repeated measures ANOVA with the within-subject factor *measurement time point* (M2, M3) and the between-subject factor *group* (NLFC on, NLFC off, NHO) were calculated for the microstate parameters. In addition, repeated measures ANOVA only with *measurement time point* (M4, M5) as a within-subject factor and with *group*

(NLFC on, NLFC off) as a between-subject factor were calculated separately for the microstate parameters. The Greenhouse–Geisser correction (Greenhouse and Geisser, 1959) was applied when necessary, and pairwise t-tests corrected for multiple comparisons were used as post-hoc tests. Two-tailed p-values are reported throughout. The alpha level for all statistical analyses was set to $\alpha = 0.05$. Effect sizes were indicated by partial eta-squares (η^2_p).

2.8. P50, N1, and P2 peak detection

The microstate analysis did not reveal distinct microstates for the P50, the N1, and the P2 (see 3.2.). This constraint notwithstanding we assessed group and measurement time point differences in the P50, the N1, and the P2 and in order to allow comparisons to previous studies who assessed P50, N1, and P2 peak amplitudes in hearing aid users (Bertoli et al., 2011; Billings et al., 2007, 2011; Easwar et al., 2015; Korczak et al., 2005; Marynewich et al., 2012; Miller and Zhang, 2014; Tremblay et al., 2006a, 2006b). For this reason we obtained AEP peak amplitudes and their respective latencies for the P50, N1, and P2 component for each participant and each measurement time point of the DEV 3 of the Ascha-Asa stimulus combination. The parameters were extracted at electrode Cz in order to directly compare the results to previous studies who also obtained the amplitudes and latencies from electrode Cz (Bertoli et al., 2011; Billings et al., 2007, 2011; Easwar et al., 2015; Korczak et al., 2005; Marynewich et al., 2012; Miller and Zhang, 2014; Tremblay et al., 2006a, 2006b). The peak latencies of the P50, the N1, and the P2 were classified in the grand average for each group and condition in order to define the latency bands for the amplitude and its respective latency extraction. According to this procedure, the maximum amplitude for the P50 was assessed in the interval of 50-150 ms after stimulus onset. For the N1, the interval of 100-200 ms after stimulus onset, and for the P2, the interval of 150-300 ms was chosen. The peaks were extracted individually by a semi-automatic procedure and confirmed by visual inspection. Analogues to the microstate statistics, the P50, N1, and P2 were then analyzed by means of a one-way ANOVA for baseline differences at M1, and with 2x3 (*measurement time point* (M2, M3) * *group* (NLFC on, NLFC off, NHO)) repeated measures ANOVA to assess the differences between hearing-impaired groups compared to NHO. Furthermore, we performed a 2x2 (*measurement time point* (M4, M5) * *group*

(NLFC on, NLFC off)) repeated measures ANOVA to obtain the differences between the NLFC on and the NLFC off groups.

2.9. Analysis of behavioral data

The accuracy of the deviant detection and the mean reaction time (RT) for correct trials were computed for each of the three DEVs for each block, for each measurement time point, and for each participant. If the accuracy was below 20%, RTs were not calculated. This was the case for DEV 1 in all stimulus blocks (see Figure 3). Thus, RTs of DEV 1 were not included in the statistical analysis. Similar to the analysis of the microstates and the P50, N1, and P2 analysis, we calculated a one-way ANOVA to assess group differences at M1, and further $2 \times 3 \times 3$ (*measurement time point* (M2, M3) * *deviant* (DEV 1 (excluded for RT), DEV 2, DEV 3) * *group* (NLFC on, NLFC off, NHO)) repeated measures ANOVA to assess the differences between hearing-impaired groups compared to NHO first, which were succeeded by $2 \times 3 \times 2$ (*measurement time point* (M4, M5) * *deviant* (DEV 1 (excluded for RT), DEV 2, DEV 3) * *group* (NLFC on, NLFC off)) repeated measures ANOVA to assess the differences between the NLFC on and the NLFC off groups. Because we did only analyze EEG measures for the DEV 3 from stimulus block Ascha-Asa (see 2.6.), we calculated the ANOVAs separately for each stimulus block to allow a direct comparison between the EEG data and the behavioral data for the stimulus block Ascha-Asa.

The ANOVAs were followed by pairwise t-tests corrected for multiple comparisons by Bonferroni correction, when appropriate. The alpha level for all statistical analyses was set to $\alpha = 0.05$. Effect sizes were indicated by partial eta-squares (η^2_p).

3. Results

The results are presented in three main parts. First, the behavioral performance is described. The second part is a description of the microstates statistics. Third, the results of the AEPs, namely the P50, the N1, and the P2, are presented. In each of the three sections, there is a first part about baseline differences between the groups at M1, a second part about the differences between the hearing-impaired and those with

normal hearing at M2 and M3, and a third part about the differences between the groups with the two distinct hearing aid features at M4 and M5.

3.1. Behavioral performance

3.1.1. The differences between hearing-impaired and normal-hearing individuals

3.1.1.1. Stimulus combination 1: Ascha-Asa

The one-way ANOVA for accuracy at M1 revealed group differences for DEV 1 ($F(2,36)=9.48$, $p<.001$) and DEV 2 ($F(2,36)=11.88$, $p<.001$), but not for DEV 3 ($p>.05$). For DEV 1 and DEV 2, post-hoc analysis showed that accuracy was higher for NHO compared to hearing impaired (all $p<.01$). The 2 (M2, M3) \times 3 (DEV 1, DEV 2, DEV 3) \times 3 (NHO, NLFC on, NLFC off) repeated measures ANOVA further revealed that there was a main effect of measurement time point ($F(1,36)=4.30$, $p=.04$, $\eta^2p=.11$) showing 3% increase of accuracy from M2 to M3 on average across all groups. The accuracy was higher for DEV 3 than DEV 2 ($p<.001$) and for DEV 2 than DEV 1 ($p<.001$) as was shown in the main effect deviant ($F(2,72)=199.06$, $p<.001$, $\eta^2p=.85$). Further, the main effect group ($F(2,36)=19.43$, $p<.001$, $\eta^2p=.52$) showed that NHO performed 23.8% better than the group with NLFC off ($p<.001$) and 25.8 % better than the group with NLFC on ($p<.001$) averaged across both measurement time points. The interaction deviant \times group ($F(3.46,62.25)=8.35$, $p<.001$, $\eta^2p=.32$) showed that the NHO group performed better than the hearing impaired, especially in the difficult deviant condition, DEV 1.

For RT, the one-way ANOVA at M1 showed that RT was different between groups for DEV 2 ($F(2,36)=10.21$, $p<.001$), but not DEV 3 ($p>.05$). More precisely it revealed that NHO performed faster than the two hearing-impaired groups (both $p<.01$) in the DEV 2 condition. The 2 (M2, M3) \times 2 (DEV 2, DEV 3) \times 3 (NHO, NLFC on, NLFC off) repeated measures ANOVA showed a significant main effect of deviant ($F(1,36)=142.41$, $p<.001$, $\eta^2p=.80$), a significant main effect of group ($F(2,36)=8.52$, $p=.001$, $\eta^2p=.32$), and a significant interaction of deviant \times group ($F(2,36)=8.35$, $p<.001$, $\eta^2p=.36$). The post-hoc tests for these effects revealed that participants detected the DEV 3 faster than the DEV 2 ($p<.001$) and that NHO performed faster than the two hearing-impaired groups

(both $p < .05$). Further, the interaction showed that the NHO performed faster than the hearing impaired, especially in the DEV 2 condition.

3.1.1.2. Stimulus combination 2: Ascha-Afa

The one-way ANOVA for accuracy did not reveal any significant differences between groups at M1. The $2 (M2, M3) * 3 (DEV 1, DEV 2, DEV 3) * 3 (NHO, NLFC \text{ on}, NLFC \text{ off})$ repeated measures ANOVA however showed that there was a significant main effect of measurement time point ($F(1,32)=4.46$, $p=.04$, $\eta^2p=.12$) revealing that the accuracy was increased from M2 to M3 (2.6 %). Furthermore, the main effect deviant ($F(1,32,42.19)=238.35$, $p<.001$, $\eta^2p=.88$) showed that DEV 3 was detected with higher accuracy than DEV 2 ($p<.001$) and DEV 2 was detected with higher accuracy than DEV 1 ($p<.001$).

For RT, the one-way ANOVA did not reveal any significant differences between groups at M1. The $2 (M2, M3) * 2 (DEV 2, DEV 3) * 3 (NHO, NLFC \text{ on}, NLFC \text{ off})$ repeated measures ANOVA for RT further showed that there was a significant main effect of measurement time point ($F(1,35)=12.11$, $p=.001$, $\eta^2p=.26$), a significant main effect deviant ($F(1,35)=137.79$, $p<.001$, $\eta^2p=.80$) and an interaction between deviant * group ($F(2,35)=3.81$, $p=.03$, $\eta^2p=.18$). Irrespective of group, the RT was shorter at M3 than M2 (22.02 ms) and DEV 3 was detected faster than DEV 2 (74.95 ms). The interaction revealed that the NHO group showed specifically faster RT as compared to the two hearing-impaired groups when detecting the easier DEV 3.

3.1.1.3. Stimulus combination 3: Afa-Asa

The one-way ANOVA at M1 for accuracy showed a significant main effect of group (for DEV 1: $F(2,35)=8.20$, $p=.001$, for DEV 2: $F(2,36)=7.14$, $p=.002$, for DEV 3: $F(2,35)=3.86$, $p=.03$) for each DEV. Post-hoc t-tests revealed that the NHO performed better than the two hearing-impaired groups for DEV 1 (both $p < .05$) and DEV 2 (both $p < .05$), while for DEV 3 there was only a trend (both $p < .01$). The $2 (M2, M3) * 3 (DEV 1, DEV 2, DEV 3) * 3 (NHO, NLFC \text{ on}, NLFC \text{ off})$ repeated measures ANOVA showed a main effect of deviant ($F(1,12,38.09)=81.34$, $p<.001$, $\eta^2p=.71$), which revealed that DEV 3 was detected with higher accuracy than DEV 2 ($p<.01$) and DEV 2 with higher accuracy than

DEV 1 ($p < .001$). The significant main effect group ($F(2,34)=8.10$, $p=.001$, $\eta^2p=.32$) further showed that the NHO performed better than the two hearing-impaired groups ($p < .01$). Moreover, there was a significant interaction between deviant and group ($F(2.24,38.09)=4.76$, $p=.01$, $\eta^2p=.22$) showing that NHO performed better especially under difficult conditions such as detecting DEV 1.

For RT, the one-way ANOVA at M1 revealed a main effect of group for both DEV 2 and DEV 3 (DEV 2: $F(2,36)=4.63$, $p=.02$, DEV 3: $F(2,35)=4.41$, $p=.02$). The post-hoc t-tests further showed that for both, DEV 2 and DEV 3, NHO performed faster than the group with NLFC on (both $p < .05$). The 2 (M2, M3) * 2 (DEV 2, DEV 3) * 3 (NHO, NLFC on, NLFC off) repeated measures ANOVA resulted in a main effect of measurement time point ($F(1,36)=5.29$, $p=.03$, $\eta^2p=.13$) leading to the conclusion that RT decreased from M2 to M3 irrespective of group or deviant. Further, the main effect deviant ($F(1,36)=6.79$, $p=.01$, $\eta^2p=.16$) revealed that DEV 3 was detected faster than DEV 2. Furthermore, there was a main effect of group ($F(2,36)=7.75$, $p=.002$, $\eta^2p=.30$) showing that the NHO performed faster than both hearing-impaired groups (both $p < .05$). The interaction between deviant and group ($F(2,34)=3.66$, $p=.04$, $\eta^2p=.17$) and the threefold interaction measurement time point * deviant * group ($F(2,36)=4.76$, $p=.02$, $\eta^2p=.21$) further showed that NHO performed faster than the hearing impaired especially while detecting DEV 2 (the more difficult deviant) and that this difference was higher at M2 than M3.

3.1.2. The effect of NLFC

3.1.2.1. Stimulus combination 1: Ascha-Asa

The 2 (M4, M5) * 3 (DEV 1, DEV 2, DEV 3) * 2 (NLFC on, NLFC off) repeated measures ANOVA for accuracy showed a main effect deviant ($F(1.18,28.4)=270.48$, $p < .001$, $\eta^2p=.92$). The post-hoc t-tests pointed to the higher accuracy for DEV 3 compared to DEV 2 ($p < .001$) and the higher accuracy for DEV 2 compared to DEV 1 ($p < .001$). The interaction measurement time point * group ($F(1,24)=5.17$, $p=.03$, $\eta^2p=.18$) showed that the group with NLFC on showed a stronger increase of accuracy from M4 to M5 compared to the group with NLFC off.

The corresponding ANOVA for RT resulted in a significant main effect of measurement time point ($F(1,24)=4.54$, $p=.04$, $\eta^2_p=.16$) and significant main effect deviant ($F(1,24)=110.45$, $p<.001$, $\eta^2_p=.82$). At M4 the two groups exposed shorter RTs (than at the follow-up measurement time point M5 (13.12 ms) and the two groups had shorter RTs to detect DEV 3 compared to DEV 1 (105.37 ms).

3.1.2.2. Stimulus combination 2: Ascha-Afa

For accuracy, the 2 (M4, M5) * 3 (DEV 1, DEV 2, DEV 3) * 2 (NLFC on, NLFC off) repeated measures ANOVA only revealed a significant main effect of deviant ($F(1.48,32.55)=191.09$, $p<.001$, $\eta^2_p=.90$) showing that accuracy was higher for DEV 3 compared to DEV 2 ($p=.001$) and for DEV 2 compared to DEV 1 ($p<.001$).

The same ANOVA for RT (without DEV 1) also resulted in a significant main effect of deviant ($F(1,24)=44.20$, $p<.001$, $\eta^2_p=.65$), but also in a significant main effect of measurement time point ($F(1,24)=4.29$, $p=.049$, $\eta^2_p=.15$) with lower RT at M4 compared to M5 (15.83 ms). Also, DEV 3 was detected faster than DEV 1 (58.14 ms).

3.1.2.3. Stimulus combination 3: Afa-Asa

The 2 (M4, M5) * 3 (DEV 1, DEV 2, DEV 3) * 2 (NLFC on, NLFC off) repeated measures ANOVA for accuracy only revealed a significant main effect deviant ($F(1.16,25.45)=89.66$, $p<.001$, $\eta^2_p=.80$) confirming that DEV 3 was detected with higher accuracy than DEV 2 ($p=.02$) and DEV 2 with higher accuracy than DEV 1 ($p<.001$) respectively.

For RT, 2 (M4, M5) * 2 (DEV 2, DEV 3) * 2 (NLFC on, NLFC off) repeated measures ANOVA showed a main effect measurement time point ($F(1,24)=4.96$, $p=.04$, $\eta^2_p=.17$) and a main effect deviant ($F(1,24)=17.37$, $p<.001$, $\eta^2_p=.42$). From M4 to M5 the reaction times decreased. Across the two measurement time points, DEV 3 was detected faster than DEV 2.

3.2. Microstates

For the DEV 3 trials, the topographic AAHC clustering revealed a total of 14 temporally stable maps over the ERP time course from 0-1200 ms as the best solution, which explained 63.81% of the global variance. For further analysis, we chose the three maps that each explained at least 10% of the total variance (see Figure 5): Map 1, corresponding to the N2b, accounted for 47% of the variance, Map 2, which is related to the frontal P3b, for 10%, and Map3, corresponding to the parietal N3b, for 24%. If a map did not occur in a participant, it was coded as a missing value. Figure 5 depicts the GFP of the grand averaged data and the temporal occurrence of these three microstates for each group and measurement time point. The three maps were subjected to further analyses, namely a re-fitting to single subject's data from 0 -1200 ms after stimulus onset.

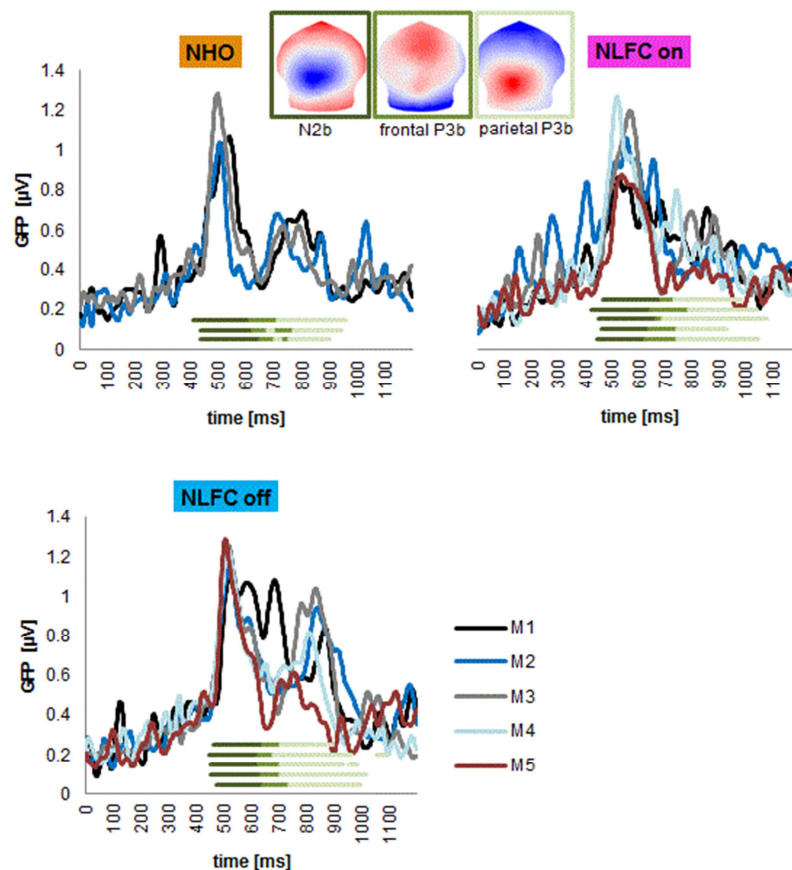


Figure 5: This graph shows the results of the microstate analysis for the difference waves of the easy deviant DEV 3 /Asa/ of stimulus block 1 minus the standard stimulus /Ascha/ of stimulus block 1. The top depicts the three representative microstate maps that explained about 60% of the global variance of the ERP time course from 0-1200 ms. The three graphs show the time course of the global field power (GFP) of the grand averaged EEG signal and in green tones the occurrence of each microstate map. These are depicted for each measurement time point as shown in the different lines with M1 starting at the bottom.

The x-axis shows time and the y-axis the GFP, separately for each group (NHO, NLFC on, NLFC off) and measurement time point (M1, M2, M3, M4, and M5).

3.2.1. The differences between hearing-impaired and normal-hearing individuals

3.2.1.1. Mean GFP

The one-way ANOVA for M1 did not reveal any significant group differences. However, for the N2b-like mean GFP, the repeated measures ANOVA (measurement time point (M2, M3) * group (NLFC on, NLFC off, NHO)) revealed a main effect of group ($F(1,29)=7.03$, $p=.003$, $\eta^2_p=.33$), showing that the NHO decreased their GFP from M1 to M2 having lower GFP at M2 and M3 than the group with NLFC off ($p=.002$), while the group with NLFC on was not different from the other two groups (both $p>.05$). The repeated measures ANOVA for the mean GFP of the frontal P3b-like microstate did not reveal any significant results. The analysis for the mean GFP of the parietal P3b showed, similar to the N2b-like microstate, a main effect of group ($F(2,36)=3.97$, $p=.028$, $\eta^2_p=.18$) revealing that the NHO decreased the GFP from M1 to M2 and had lower GFP at M2 and M3 compared to the group with NLFC off ($p=.024$) at M2 and M3, while the group with NLFC on was not different from the other groups (both $p>.05$). See Figure 6 for changes in the mean GFP of all microstates analyzed here.

3.2.1.2. Latency of peak GFP

The one-way ANOVA for M1 did not reveal any significant group differences in the latency of the peak GFP for the three microstates. Neither did we find any modulations across measurement time points for the latency of the peak GFP of the three microstates.

3.2.2. The effect of NLFC

3.2.2.1. Mean GFP

The repeated measures ANOVA (measurement time point (M4, M5) * group (NLFC on, NLFC off)) for the mean GFP of the N2b-like microstate did not reveal any

significant differences. The analysis for the frontal P3b-like microstate showed that there was a main effect measurement time point ($F(1,18)=41.26$, $p<.001$, $\eta^2_p=.70$), revealing that the mean GFP of the frontal P3b-like microstate decreased from M4 to M5. Further, there was an interaction of measurement time point * group ($F(1,18)=5.26$, $p=.03$, $\eta^2_p=.23$), showing that the decrease of the mean GFP of the frontal P3b-like microstate was stronger for the group with NLFC on compared to the group with NLFC off. Additionally, the mean GFP of the parietal P3b-like microstate also decreased from M4 to M5 ($F(1,20)=7.91$, $p=.01$, $\eta^2_p=.28$).

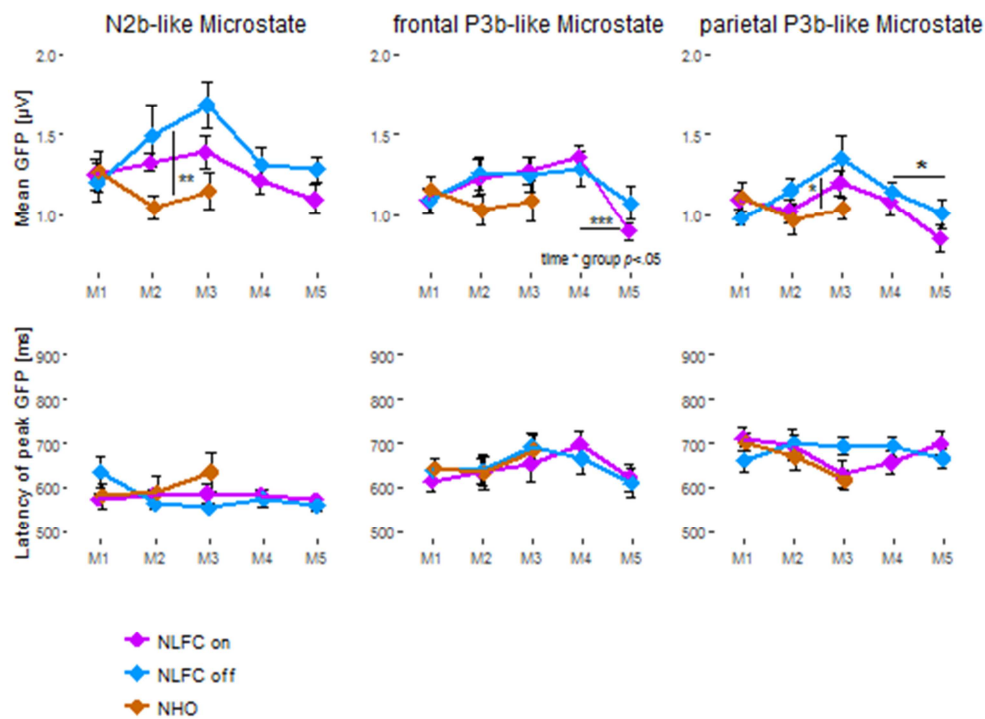


Figure 6: The upper row shows the mean global field power (GFP) of each microstate (N2b-like, frontal P3b-like, and parietal P3b-like), separately for each measurement time point (M1, M2, M3, M4, and M5) and each group (NLFC on, NLFC off, and NHO), while the lower row shows the peak latency of the GFP.

3.2.2.2. Latency of peak GFP

For the latency of the peak GFP, we found no significant modulations.

3.3. P50, N1, P2 peak amplitude results

The ERPs from electrode Cz for the easy deviant DEV 3 of the stimulus combination Ascha-Asa are depicted in Figure 7, and the descriptive data of the peak and latency of the P50, the N1, and the P2 are described in Table 1.

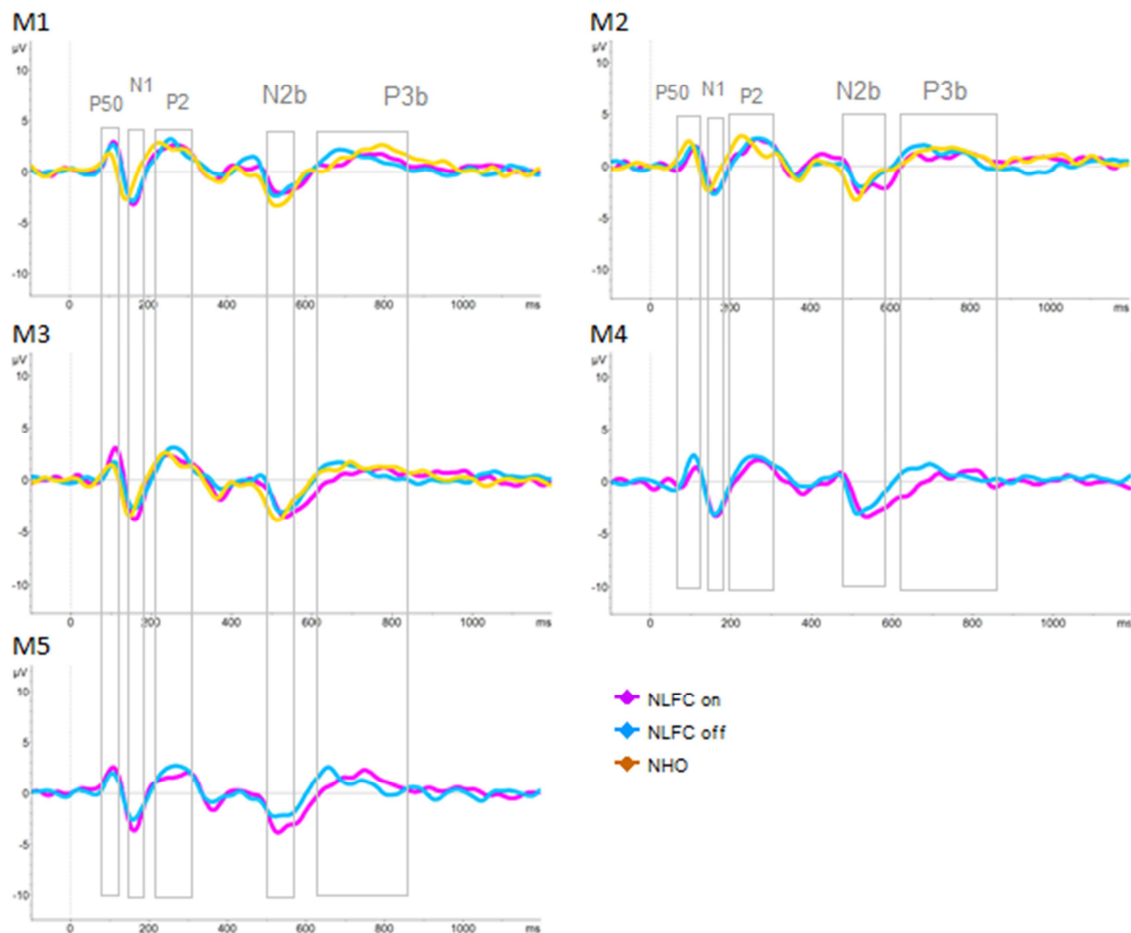


Figure 7 shows the ERP data derived from electrode Cz for the easy deviant DEV 3 /Asa/ of stimulus block 1, separately for each group (NLFC on in pink, NLFC off in blue, NHO in gold) and each measurement time point (M1, M2, M3, M4, and M5) for visual inspection.

Table 1: Means and standard deviations of P50, N1 and P2 amplitudes and latencies derived from electrode Cz, separately for each group and measurement time point. *Note* M= Mean, SD = Standard Deviation.

	Group	P50 Latency		P50 Amplitude		N1 Latency		N1 Amplitude		P2 Latency		P2 Amplitude	
		M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
M1	NLFC on	103.54	18.94	2.88	1.34	161.85	7.89	-3.35	1.74	262.46	20.30	3.80	2.07
	NLFC off	109.08	9.15	2.81	1.37	159.23	7.73	-2.89	2.97	273.23	34.76	3.62	1.54
	NHO	92.77	16.62	2.19	1.11	139.69	9.01	-2.83	1.61	258.15	36.46	3.57	2.14
M2	NLFC on	107.54	16.68	2.14	1.24	161.54	16.64	-3.01	1.57	272.31	33.76	3.56	1.42
	NLFC off	99.54	18.76	2.23	1.31	160.00	12.06	-3.02	2.38	268.31	29.27	3.47	1.75
	NHO	92.00	15.10	2.44	0.94	144.92	13.33	-2.48	2.12	252.00	45.02	3.42	1.88
M3	NLFC on	109.08	5.51	2.81	1.53	158.46	8.76	-3.85	2.07	267.23	27.73	3.70	2.04
	NLFC off	104.00	21.69	1.80	1.07	159.23	14.62	-3.09	3.43	255.38	24.80	3.36	2.35
	NHO	95.08	17.14	1.63	1.35	142.77	8.93	-3.46	2.47	244.92	29.32	3.30	2.79
M4	NLFC on	94.46	24.90	2.75	1.67	162.46	6.44	-3.67	2.14	272.31	36.04	2.89	1.32
	NLFC off	102.00	22.23	2.47	1.27	156.77	18.66	-2.74	3.08	264.15	27.25	3.39	2.67
M5	NLFC on	107.54	16.58	1.78	1.06	161.85	13.89	-3.62	2.30	267.85	29.48	2.58	1.16
	NLFC off	106.15	8.22	2.59	1.66	159.23	14.93	-3.27	3.54	274.77	29.99	3.34	2.84

3.3.1. The differences between hearing-impaired and normal-hearing individuals

The one-way ANOVA for M1 showed that there was a main effect of group for the P50 latency ($F(2,36)=3.73$, $p=.03$) and for the N1 latency ($F(2,36)=28.13$, $p<.001$) revealing that the NHO displayed shorter P50 latencies as compared to the group with NLFC off ($p<.05$) and shorter N1 latencies as compared to both hearing-impaired groups (both $p<.001$). The repeated measures ANOVA (measurement time point (M2, M3) * group (NHO, NLFC on, NLFC off) for the P50 revealed a significant interaction ($F(2,36)=3.97$, $p=.03$, $\eta^2_p=.18$) showing that for the group with NLFC off and the NHO there was a decrease of amplitude from M2 to M3, while for the group with NLFC on, there was an increase. For the P50 latency there was a main effect of group ($F(2,36)=4.37$, $p=.02$, $\eta^2_p=.20$) revealing that across M2 and M3 the P50 latency was longer for the hearing-impaired compared to the group with normal hearing ($p<.05$). The repeated measures ANOVA for the N1 amplitude resulted in a significant effect of measurement time point ($F(1,36)=5.05$, $p=.03$, $\eta^2_p=.12$) showing that irrespective of group, the amplitude increased from -2.84 to -3.47 μV . For the N1 latency, there was again a main group effect ($F(2,36)=9.59$, $p<.001$, $\eta^2_p=.35$) similar to the P50 latency, showing that NHO had shorter latencies than both hearing impaired groups (both $p<.01$). For the N2 latency and amplitude there were no significant effects.

3.3.2. The effect of NLFC

The analysis for the P50, N1, and P2 amplitudes and latencies did not reveal any significant effects.

4. Discussion

In this paper we examined longitudinal modulations of early sensory-driven and later cognitive-related auditory processing and its modulations by hearing loss and hearing aid treatment in healthy, older adults. Traditionally, studies investigated the effects of hearing aid amplification only at initial stages of hearing, namely for the P50, N1, and the P2 in young adults. Decreases or increases in amplitudes and longer latencies in aided when compared to unaided situations are usually reported (Billings et al., 2007, 2011; Marynewich et al., 2012; Miller and Zhang, 2014; Tremblay et al., 2006a). The direct investigation of auditory plasticity in an older age group, the group mostly affected by presbycusis, ensures the applicability of the study results in the clinic. By applying a research design with repeated EEG testing of normal-for-age hearing older adults and hearing aid users in the lab, it was possible to describe auditory plasticity across three months. During these three months, hearing-impaired participants were required to have their hearing aids switched on in their everyday life for at least eight hours each day. Furthermore, all participants had at least one year's hearing aid experience, which minimized the potential biases involved when experiencing a hearing aid for the first time. We follow with a comprehensive discussion of the results and their implications.

4.1. Delayed auditory plasticity in hearing-impaired compared to normal-hearing older adults

Previous studies have demonstrated differences in auditory cortical representations in aided compared to unaided listening conditions (Bertoli et al., 2011; Billings et al., 2011; Marynewich et al., 2012; Tremblay et al., 2006a), when participants were passively presented with auditory stimuli. In the present study, the participants actively listened to speech syllables while performing a deviant detection task. This task evokes not only early AEPs, but also the later occurring N2b and the P3b event-related

component, which allows the study of longitudinal plasticity in both early auditory processing and also cognitive-related auditory processing as a function of hearing loss. In line with previous studies (Korczak et al., 2005; Marynewich et al., 2012; Miller and Zhang, 2014) and in accordance with our hypothesis, there were no group differences in the P50, N1, and P2 peak amplitudes between hearing aid users and normal-hearing listeners. Furthermore, at M1, there were no significant group differences in the GFP of the N2b-like, the P3b-like and the LPP-like microstates. Instead, and in line with our hypothesis, we found slightly longer latencies in hearing aid users compared to normal-hearing older adults in the P50 and the N1 across all measurement time points, as was also shown in previous within-subject studies with younger adults (Marynewich et al., 2012; Miller and Zhang, 2014). This delay in the early cortical processes has partially been attributed to the time consumed by signal processing in the hearing aids, which takes about 4.5 ms (Miller and Zhang, 2014) and leads to a total delay of approximately 10 ms in the brain. These delays did not occur any more in the later P2 peak latency, or in the N2b-like or P3b-like microstates GFP peak latencies. In other words, the delay of the initial perceptual processing apparently did not affect later cognitive processing. Furthermore, previous within-subject studies have reported that behavioral RTs are shorter in aided compared to unaided listening situations in hearing-impaired (Downs, 1982; Gatehouse and Gordon, 1990), which means that in total, the latency delay of early AEPs, occurring due to the signal processing time, does not reverse the overall effect of hearing aids which lead to a decrease of behavioral RT.

Differences in RTs between aided and unaided conditions have also been related to (listening) effort (Downs, 1982; Gatehouse and Gordon, 1990). For example, it was shown that the (listening) effort was decreased in hearing-impaired individuals with the use of hearing aids (Downs, 1982; Gatehouse and Gordon, 1990). In this between-subject design, we found longer RTs in the hearing-impaired compared to the normal-hearing older adults when they correctly identified deviant stimuli. This finding confirms previous results which demonstrated that unaided poorer listeners show longer RTs in an auditory n-back task compared to unaided better listeners (Frtusova and Phillips, 2016). This was considered to be an effect of higher perceptual demands and therefore higher perceptual effort in the group with poorer hearing (Frtusova and Phillips, 2016). The assumption that higher perceptual effort leads to longer RTs in older hearing-impaired is further supported by the finding that these RT delays are modality

specific and are not found in the visual domain (Frtusova and Phillips, 2016). In addition, we matched our three experimental groups in IQ as measured by the KAI test (Lehrl, 1992), which incorporates visual processing speed as a subtest. This further promotes the interpretation that the longer RTs reflect higher perceptual demands specifically for the auditory domain. In general, the lower accuracy in the group with hearing impairment also suggests the possibility that perceptual demands were higher for the hearing-impaired compared to those with normal hearing.

The other core research focus of this work was to evaluate the possible differences in longitudinal auditory plasticity between the hearing-impaired and those with normal hearing. Behaviorally, all groups increased in accuracy and decreased in RT with repeated testing reflecting decrease in perceptual effort. However, the electrophysiological data showed that in the normal-hearing group the GFP of the cognitive N2b-like and P3b-like microstates at measurement time point two (after two weeks) decreased, while the same decrease of GFP was only found at measurement time point 5 (after twelve weeks) in the two hearing-impaired groups. This finding could suggest lower auditory plasticity in the hearing impaired-group compared to the normal-hearing group. The rationale behind this is that, with repeated testing, it is expected that the task will get easier and therefore requires less effort. Less required effort should result in a decrease of brain activation as a function of lower neural resources that are needed to perform the task. Here, we used GFP of microstates as a reflection of the global brain activation of three distinct neural processes: First, the auditory categorization of a deviant stimulus as flagged by the N2b-like microstate (Näätänen and Gaillard, 1983; Simson et al., 1977), and second, the memory updating (Debener et al., 2002; Kok, 1997; Polich, 2007; Volpe et al., 2007) as reflected in the P3b-like microstate. In other words, we argue that the delayed decrease of activation strength in all of these microstates in the hearing-impaired is correlated with a delayed decrease of (perceptual) effort during auditory categorization and memory updating. In order to more clearly define the term (perceptual) effort, we use the term processing effort which is defined as the additional resources allocated to a listening task in order to meet the task goal under adverse listening conditions (Lemke and Besser, 2016). To date, several behavioral studies have shown that hearing aids can decrease processing effort in auditory tasks when compared to unaided conditions (Hällgren et al., 2005; Hornsby, 2013; Rudner, 2016; Tremblay and Backer, 2016). The present study supports

these findings by providing neurophysiological evidence that the hearing-impaired do not only immediately show higher processing effort, but that they also need more exposure to auditory stimuli after being fitted with a new hearing aid algorithm to decrease their processing effort across time.

Several behavioral studies have so far used cognitive measures as outcome variables when comparing aided to unaided listening situations in older adults. For example, performance in working memory, as assessed by the auditory reading span test, was higher when participants were aided (Doherty and Desjardins, 2015). Furthermore, hearing aid users improved in dichotic listening tasks after eight weeks of being exposed to the acoustic environment through the hearing aid, while controls did not (Lavie et al., 2015). These findings suggest that hearing aids facilitate not only perceptual auditory processes, but also cognitive-related auditory processes. For the purpose of better understanding possible hearing aid benefits in cognitive-related auditory processing, we assessed not only early perceptual evoked-potentials such as the P50, N1, and P2, but also the auditory N2b/P3b event-related potentials as markers for cognitive-related auditory processing. The N2 has been described as a neural marker for the auditory categorization of phonetically deviant stimuli (Näätänen and Gaillard, 1983; Simson et al., 1977) and the P3 as a neural marker for attention and memory updating (Debener et al., 2002; Kok, 1997; Polich, 2007; Volpe et al., 2007).

Interestingly, the studies described above have linked the cognitive benefits of hearing aids to lower cognitive effort (Doherty and Desjardins, 2015). Other research has also shown that hearing aids reduced the extra cognitive effort needed to successfully understand speech (Desjardins and Doherty, 2013, 2014). In an attempt to better define cognitive effort in the context of speech processing, similar to above, we again used the term processing effort to describe the additional resources allocated to the auditory task in order to meet the task requirements (Lemke and Besser, 2016). Furthermore, the authors describe “brain over-activation” as a potential neural correlate for higher processing effort (Lemke and Besser, 2016). Thus, in this study we obtained the GFP of the event-related potentials to serve as a global measure for brain activation and therefore also as a correlate of processing effort.

4.2. Acclimatization to specific hearing aid feature takes several weeks

As a third research question, we intended to test different hearing aid features against each other regarding their effect on auditory plasticity. We predicted that NLFC would increase performance in hearing-impaired older adults more strongly than pure amplification across the three months of study duration (Alexander, 2016; Wolfe et al., 2011, 2015). At the same time, several studies demonstrated that some hearing aids decreased processing effort (Hällgren et al., 2005; Hornsby, 2013; Rudner, 2016; Tremblay and Backer, 2016), which led us to the hypothesis that NLFC would reduce processing effort of high pitched fricatives more strongly than pure amplification by increasing audibility of fricatives. In this study, we could find a stronger increase of accuracy from M4 to M5 in the group with NLFC on compared to the group with NLFC off in the stimulus block Ascha-Asa (the same from which the EEG data was processed), although the two groups improved their performance across time. Previous studies also found behavioral improvements across several months of using NLFC, namely decreases in the thresholds for the correct identification of syllables (Wolfe et al., 2011, 2015). Notably, it is difficult to attribute these effects solely to the use of NLFC, because these studies neglected to collect control group data. Interestingly, in our study, we found a similar interaction in the neurophysiological data, namely a stronger decrease of GFP of the P3b-like microstate, a flag for decrease of processing effort, in the group with NLFC on. Furthermore, we found a higher GFP in the N2b-like and the parietal P3b-like microstate in the normal-hearing group compared to the group without NLFC at measurement time points two and three, while the group with NLFC did not differ significantly from the other two. Interpreting the differences in GFP again in the framework of processing effort (as described in the previous section) (Lemke and Besser, 2016) leads to the conclusion that the group without NLFC demonstrated higher processing effort than the normal-hearing group, while the group with NLFC did not differ in terms of processing effort from the normal-hearing group. This means that the improvement of audibility of the fricatives provided by the NLFC algorithm decreases the processing effort of these fricatives. The second set of differences in the neurophysiological parameters found was in line with our predictions, namely that the brain needed several weeks to acclimatize to a new hearing aid feature. This was indicated by the differences in GFP between the group with NLFC on compared to NLFC off only at measurement time point five in the frontal P3b-like microstate. Based on this

finding, we conclude that an older brain over the age of 60 years needs more time than expected to adapt to a new hearing aid feature.

4.3. Limitations

The current study design did not allow for the complete disentanglement of the sole effects of hearing aids acclimatization and the sole effects of hearing loss on auditory plasticity. In order to take this into account, we would have needed an additional control group, namely a group with moderate hearing loss, which would have remained untreated during the study period of three months. We agreed that this would have been an unethical study procedure.

Furthermore, the paradigm could be optimized in the future in order to also look at differences in more difficult deviants, which would be possible when using more trials per condition. However, this means that the tasks would increase in time to perform, which is not feasible for older study participants.

4.4. Conclusions

Through the application of a longitudinal EEG approach, we examined auditory plasticity in two hearing-impaired groups using different hearing aid features, and in normal-hearing healthy older adults. Compared to previous studies which investigated the effect of hearing aids in normal-hearing younger adults (Billings et al., 2007, 2011; Marynewich et al., 2012; Miller and Zhang, 2014; Tremblay et al., 2006a), our findings are transferable to an older population, the one mostly suffering from age-related hearing loss. The novel result of this study is that the hearing-impaired demonstrated higher auditory processing effort (as indicated by the higher GFP in the N2b, P3b, and the LPP) and an accordingly delayed cognitive-related auditory plasticity when compared to those with normal hearing. In other words, the hearing-impaired individuals needed more exposure to the auditory stimulus material in order to decrease the electrophysiological activity that flags processing effort. In general, we also demonstrated that low-level auditory treatment provides a scaffolding to higher cognitive functioning, as shown by the GFP differences of the P3b and LPP between the group with NLFC on compared to the group with NLFC off. An additional note to this

context is that at least twelve weeks are required for an older brain to adapt to such a new hearing environment.

3. General Discussion

3.1. Discussion of the most important findings

In the next section, the aims of this PhD thesis will be reiterated and the findings summarized. This will be followed by a discussion of the implications for older adults with age-related hearing loss, and an outline for future directions in related research.

Aim I: Developing a test battery to assess central hearing loss in older adults. In Study I, we assessed central hearing loss through implementing a variety of psychoacoustic tasks (Giroud et al., under review; Kegel et al., in preparation). We obtained temporal and spectral processing as two parameters which needed to be encoded into a speech signal, and added a speech in noise sentence understanding task to evaluate central hearing performance. The tasks were adaptive, comprised a reliable number of trials, and were controlled for the individual audibility thresholds as well as for false positives. Our results showed that central hearing loss was evident in peripherally normal hearing older adults, independent of their individual hearing thresholds. This is in line with previous research showing that older adults have reported having speech processing problems even when their peripheral hearing was normal (Füllgrabe, 2013; Füllgrabe et al., 2015; Hopkins and Moore, 2011; Moore et al., 2014; Pichora-Fuller and Souza, 2003). It is therefore recommended that clinicians use supra-threshold and cognitive hearing tasks to better assess the complexity of hearing problems in older adults. Furthermore, researchers who study the hearing of older adults should not only assess peripheral hearing thresholds, but also include central hearing measures when assigning older adults to groups of good and poor hearers. By taking both peripheral and central hearing problems into account, future researchers will be better able to accurately estimate the severity and health consequences of hearing loss in older adults, effects which currently tend to be underestimated.

Aim II: Describing neural correlates of central hearing loss. This PhD thesis was one of the first worldwide to describe multimodal neural fingerprints of central hearing loss as assessed through the supra-threshold tasks explained above. We assessed both the structural and intrinsic functional data, while our selection of neural

parameters was based on recent theories regarding parameter-based neural speech processing (Giraud et al., 2007; Giraud and Poeppel, 2012a; Morillon et al., 2010; Poeppel, 2001, 2003a). Study I provided descriptions of the age-related differences in cortical thickness, and the relation of these differences to central hearing performance. Difficulties in speech processing are therefore not only caused by peripheral damage, but may also be related to cortical thinning in the right auditory areas across the lifespan. Those older adults with thicker right auditory areas performed better in the hearing tasks. This relation was not evident in the frontal brain structures, which are more strongly related to cognitive processes. Interestingly, this finding partially throws into question the widely-known idea that it is the frontal lobe which compensates for sensory decline in older adults (Cabeza et al., 1997; Grady et al., 1994). The research behind this notion hypothesizes that increased activity in the prefrontal lobe in older brains, as compared to younger brains, relates to compensatory mechanisms for age-related decline in sensory regions (Cabeza et al., 1997; Grady et al., 1994). However, the frontal lobe also has the highest rate of atrophy (Fjell et al., 2009; Raz et al., 2005; Resnick et al., 2003) and it is thus not yet clear how a structure like the prefrontal lobe, which is most affected by age, would be able to compensate for sensory areas that may have been less subjected to age-related decline. Our results add further support to this critical notion, as our data did not show that the relation between cortical thickness of frontal areas and the hearing performance was moderated by age. Thus, there is a need for future research to focus on this question in more detail to better understand this inconsistency in the literature.

Thicker right auditory areas were also related to stronger right-lateralized theta power. Thicker right auditory areas may therefore allow for an increase in the power of their intrinsic oscillatory functioning, which is mainly in the theta band in the right auditory areas (Giraud and Poeppel, 2012a; Poeppel, 2001, 2003a), due to the possibility of activating more synapses. This in turn may be interpreted as an intrinsic imprint of the stronger reliance on suprasegmental acoustic cues observed in older adults. Such a reliance has been shown previously by behavioral research, in which older adults relied more on prosodic cues to understand speech than younger adults did (Giroud et al., in preparation; Steinhauer et al., 2010; Wingfield et al., 1992, 2000).

Aim III: Designing a longitudinal study using central and cognitive hearing as outcome variables. In Study II, we established a longitudinal design by assessing central hearing behaviorally and neurally as outcome variables. We created stimulus material comprising of speech syllables and validated the design in a young sample of normal hearing adults. Study II was the basis for Aims IV-VI as investigated in Study III.

Aim IV: Describing how hearing aids and hearing impairment in older adults affect central and cognitive hearing and their underlying neural functioning. In Study III, we investigated older hearing aid users with moderate age-related hearing loss and compared them to older adults without hearing loss regarding the neural processes that reflect central hearing during speech processing. The results showed that hearing impairment led to a lower auditory performance, especially in difficult conditions. To assess neural effort, we matched behavioral performance between the three groups and assessed the global field power of perceptual and cognitive processing stages of the speech syllables. We found that hearing impaired groups invested more neural effort to get to the same performance level as the normal hearing, age-matched group. Furthermore, our results did not show any group differences between the hearing impaired groups which used different hearing aid algorithms. Thus, no benefit of one particular hearing aid algorithm was evident in this cross-sectional analysis.

Aim V: Describing how hearing aid use and moderate hearing impairment in older adults affect behavioral and neural plasticity during longitudinal auditory learning. For Study III, it was particularly important to challenge previous research designs which included only younger adults in order to exclude the possible confounding influence of central hearing loss in older adults (Billings et al., 2007, 2011; Marynewich et al., 2012; Miller and Zhang, 2014; Tremblay et al., 2006a). Further to this, it has been indicated that “...the inclusion of people with hearing loss who wear hearing aids is still quite sparse” (Tremblay et al., 2014b). Moreover, previous studies applied cross-sectional designs which do not allow for the study of the modulations in hearing aid benefit across time (Billings et al., 2007, 2011; Marynewich et al., 2012; Miller and Zhang, 2014; Tremblay et al., 2006a). This PhD thesis accepted the challenge described above, namely that normal hearing individuals decreased neural effort at measurement

time point two, while those with hearing impairment also decreased neural effort but only showed this learning effect at measurement time points four and five. To summarize, hearing impairment led to delayed behavioral and auditory plasticity. This finding needs to be taken into account in the approaches to training and treatment of hearing impaired older adults.

Aim VI: Assessing how long the brain needs to acclimatize to a new hearing aid algorithm. It is already known that a hearing aid algorithm may take time to have an impact, and that individuals need to accumulate acoustic experience to benefit from a new hearing aid algorithm (Alexander, 2016; Wolfe et al., 2011, 2015). Our data suggests that this acclimatization may take about 6-12 weeks of intensive hearing aid use for older adults to benefit.

3.2. Implications – what can hearing impaired individuals and clinicians learn from this PhD thesis?

Several results from this PhD thesis have practical relevance. It was demonstrated that hearing loss in older adults exists without peripheral damage to the cochlea. Therefore, this thesis suggests that audiologists use supra-threshold tasks to evaluate hearing problems which are not caused by peripheral age-related damage and cannot be obtained by taking an audiogram. Although there are no treatment possibilities available for central hearing loss at the moment, one strategy which could be immediately applied would be to focus on the suprasegmental aspects of speech, such as prosody. However, this idea needs to be confirmed in future studies, one of which is currently performed in extension to this PhD thesis.

The results of this PhD thesis also showed that the use of hearing aids is beneficial to hearing impaired individuals. However, it is important to decide early (i.e., before peripheral hearing loss progresses) whether hearing aid treatment is necessary.

Otherwise, it may be the case that the brain will need a longer period of time to adapt to the new hearing aid. In addition, when deciding to change the hearing aid algorithm, it is important to acknowledge that the adaptation process is long. This knowledge may lessen the chances of early disappointment. For example, in one experiment of this PhD thesis it was shown that the participants needed to use their hearing aids intensively for approximately 12 hours every day over a period of 12 weeks before their brains adapted to the new hearing experience.

3.3. Future directions

Within the Alzheimer's and mild cognitive impairment (MCI) research community, it is notable that there is a growing discussion regarding the possible contribution of sensory decline in the development of Alzheimer's. Traditionally, MCI has been related to impairment in cognitive functions (Albert et al., 2011). However, recent research has shown that sensory decline may play an important role in the emergence of MCI or Alzheimer's dementia (AD) as well (Albers et al., 2015; Devanand et al., 2008; Gates et al., 2008, 2011; Lin et al., 2011; Pichora-Fuller et al., 2013). This PhD thesis provides a scientific basis from which to explore to what extent auditory performance may be predictive of MCI by describing several forms and neural markers of hearing loss in older adults.

To date, only few studies have investigated this issue. Thus, future research should investigate the sensory and cognitive interface in a high number of MCI and healthy controls by assessing several cognitive factors and a variety of sensory tasks for the auditory domain, such as has been presented here in this PhD thesis. Although longitudinal changes are the most predictive of MCI (Albers et al., 2015), screening for MCI in the clinic is usually restricted to cross-sectional information about the patient. Thus, cross-sectional studies are required to find the best predictors for MCI. The correlative nature of such studies has so far indicated that, in addition to cognitive decline, sensory deficits also emerge in MCI (Devanand et al., 2008). However, it is unclear whether sensory processing and cognition both decline as a function of aging and therefore have a common cause (Lindenberger and Baltes, 1994), or whether they interact or influence each other. To illustrate, Study III of this PhD thesis showed that

hearing loss negatively influenced longitudinal cognitive-related cortical plasticity in older adults. Thus, it is clear that longitudinal studies are imperatively needed to better understand the extent to which sensory changes precede cognitive decline. Furthermore, in Study I of this PhD thesis we were also able to show that the extent of cortical thinning in cortical auditory areas was related to central hearing loss in older adults. Thus, a future project should investigate between-person, but also within-person, coupled changes of sensory and cognitive performance in MCI patients and healthy older adults, while testing neuroanatomical and intrinsic neurofunctional markers (as tested in this PhD thesis) as moderators for this relationship.

One promising basis from which to build interventions for central hearing loss in healthy older adults or MCI patients is to explore the benefits of multisensory integration. Outside of the lab, many older adults do not rely exclusively on audition, but also on other modalities during speech processing. Most commonly, older adults use lip reading to better understand speech in adverse listening conditions. Several studies have compared younger and older adults' auditory recall performances and how they change when speech is accompanied by mouth movements that are in synchrony with the auditory information (Sekiyama et al., 2014; Thompson, 1995; Thompson et al., 2007). In normal hearing adults (as evaluated by peripheral hearing only), it has been shown that aging led to a larger dependence on visual articulatory movements in auditory-visual speech perception (Sekiyama et al., 2014). Older adults were actually able to improve their recall performance by using lip reading, up to the same level as younger adults (Thompson et al., 2007), while other studies have shown that audiovisual integration facilitated a working memory task in older adults, but only to the same extent as in younger adults (Frtusova et al., 2013).

At present, it is unclear how the phenomenon described above can be explained. In order to close this gap, the next step would be to explore the mechanisms underlying listening and motor activity simultaneously. Interestingly, previous studies have shown that increased activity in motor areas, even without visual cues, can compensate for hearing difficulties in older adults (Du et al., 2016). Furthermore, a recent theory suggests that, across all languages studied to date, the mouth motions and the acoustic envelope of speech typically fall within the range of 3-8 Hz. This frequency range is related to the rate of syllable production and is critical to speech perception as explained

in this PhD thesis (Chandrasekaran et al., 2009; Ghazanfar and Takahashi, 2014). Intelligibility decreases when the auditory stream is disrupted (Elliott and Theunissen, 2009; Ghitza and Greenberg, 2009; Saberi and Perrott, 1999; Smith et al., 2002) and also at the disruption of the visual stream, the visual signal from facial movements (Vitkovitch and Barber, 1996). Based on the tight correlation between the rhythms of the mouth movements and the acoustic output (Ghazanfar, 2013), we hypothesize that these synchronize during multisensory integration as reflected by entrained neural oscillations (Park et al., 2016). By means of neural entrainment as described by the AST hypotheses (Giraud and Poeppel, 2012b; Poeppel, 2003b), the auditory neurons of the brain start to entrain to the rhythms of the speech envelope, while the same rhythmic information of visual cues can be integrated whenever the auditory envelope information is difficult to follow due to hearing loss or due to cognitive impairments, for example.

As described above, the functional underpinnings of the multimodal benefit for speech intelligibility has not yet been investigated thoroughly. An approach to extend previous frameworks would be to study the oscillatory interaction between speech intelligibility and lip reading in older adults with hearing impairment and hearing aid treatment. This may prove valuable if training in lip reading can be identified as a beneficial approach in the treatment of central hearing loss.

4. References

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5. Curriculum Vitae

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EDUCATION

- 07/2013-09/2016 **PhD student**, University of Zurich, Research Unit of Neuroplasticity and Learning in Healthy Aging [summa cum laude]
 PhD thesis: *Dynamics of Electrophysiology and Morphology in Older Adults with Age-Related Hearing Loss* (Defense: Sept 23rd 2016; Advisors: Prof. Martin Meyer, Prof. Volker Dellwo, Prof. Moritz Daum)
- 07/2013-09/2016 **PhD program**, International Max Planck Research School «The Life Course: Evolutionary and Ontogenetic Dynamics»
 A joint international PhD program with the Max Planck Institute for Human Development, the Freie Universität Berlin, the Humboldt-Universität zu Berlin, the University of Michigan, the University of Virginia, and the University of Zurich
- 09/2010-01/2013 **Master of Science in Psychology**, University of Zurich [summa cum laude], Major subject: Neuroscience and Cognitive Psychology
 Master thesis: *Speech rhythm decoding in the auditory system of the brain during second language acquisition: Evidence from behavioral and electrophysiological data* [grade: excellent]
- 09/2006-09/2010 **Bachelor of Science in Psychology**, University of Zurich
 Bachelor thesis: *The autobiographical memory: What period of life is remembered best?* [grade: very good]

ACADEMIC POSITIONS

- 10/2016-01/2018 **Postdoctoral researcher**, Research unit Neuroplasticity and Learning in the Healthy Aging Brain, University of Zurich (Advisor: Prof. Martin Meyer)
- 07/2013-09/2016 **PhD student**, Research unit Neuroplasticity and Learning in the Healthy Aging Brain, University of Zurich (Advisor: Prof. Martin Meyer)

- 04/2013-10/2013 **Research assistant**, MINT-learning center, ETH Zurich (Advisors: Prof. Elsbeth Stern, Dr. Ralph Schumacher)
- 01/2013-06/2013 **Research assistant**, Research unit Neuroplasticity and Learning in the Healthy Aging Brain, University of Zurich (Advisors: Prof. Martin Meyer)
- 09/2011–03/2013 **Research assistant**, Chair for Research on Learning and Instruction, ETH Zurich (Advisors: Dr. Daniela Nussbaumer, Prof. Elsbeth Stern)
- 01/2011-01/2011 **Test leader**, Institute for Educational Evaluation, University of Zurich (Advisor: Dr. Nicole Bayer)

PUBLICATIONS FOR PEER-REVIEWED SCIENTIFIC JOURNALS

Giroud, N., Lemke, U., Reich, P., Matthes, K. L., & Meyer, M. (2017). Longitudinal auditory learning facilitates auditory cognition as revealed by microstate analysis. *Biological Psychology*, 123, 25–36. <https://doi.org/10.1016/j.biopsycho.2016.11.007>

Giroud, N., Hirsiger, S., Muri, R., Kegel, A., Dillier, N., & Meyer, M. (under review for *Brain Structure and Function*). *Neuroanatomical and intrinsic cortical oscillatory correlates of central hearing loss in older adults*.

Giroud, N., Lemke, U., Reich, P., & Meyer, M. (under review for *Hearing Research*). *The impact of hearing aids and hearing loss on auditory plasticity across three months – an electrical neuroimaging study*.

Giroud, N., Lemke, U., Reich, P., Bauer, J., Widmer, S., & Meyer, M. (under review for *European Journal of Neuroscience*). *Auditory learning in repeated listening situations: A comparison between middle-aged and older normal hearing adults*.

Kegel, A., Giroud, N., Keller, M., Meyer, M., & Dillier, N. (in prep. for *Ear and Hearing*). *Differences in Supra-Threshold Measures in Young and Elderly Adults*.

Meyer, M., Jagoda, L., Neff, P., Kleinjung, T., & Giroud, N. (in prep. for *Frontiers in Aging Neuroscience*). *Tinnitus distress is related to impaired speech in noise performance and higher peak latencies in an oddball paradigm*.

Giroud, N., Hirsiger, S., Keller, M., Kegel, A., Dillier, N., Dellwo, V., & Meyer, M. (in prep. for *Cerebral Cortex*). *Prosody – the most useful acoustic cue for older adults with central hearing loss? Bridging the gap between brain structure, brain function and central hearing*.

Kliesch, M., Giroud, N., Schreier, D., Meyer, M. (in prep. for *Brain and Language*). *Learning a New Language in Old Adulthood – A Longitudinal Study*.

Giroud, N., Kurthen, I., Dellwo, V., & Meyer, M. (in prep. for *Brain and Language*). *Temporal fine structure processing in older adults: Beyond the syllable boundary*.

BOOK CHAPTERS

Kliesch, M., Giroud, N., Pfenninger, S., & Meyer, M. (in press). 'The third age in second language acquisition'. Bristol: Multilingual Matters. *Research on Second Language Acquisition in Old Adulthood: What We Have and What We Need*.

Meyer, M., Keller, M., & Giroud, N. (in press). 'The Oxford Handbook of Voice Perception'. Oxford: Oxford University Press. *Speech Prosody Contributions of Paralinguistic Voice Features to Linguistic Dimension of Speech*.

PEER-REVIEWED CONFERENCE ABSTRACTS

Giroud, N., I., Dellwo, V., & Meyer, M. (2013). Don't let time outrun you: The influence of age on temporal information during speech processing [Abstract]. *Clinical EEG and Neuroscience*, 44(4), E1-E121.

ORAL CONTRIBUTIONS

Invited talks to conferences

Giroud, N., & Kegel, A. (2016, November). *Lower speech intelligibility in older adults - The aging ear or brain?* Invited talk for the ARCHES Meeting, Zurich, Switzerland.

Giroud, N. (2016, May). *Longitudinal auditory plasticity in older hearing aid users*. Invited talk for the Symposium Audition, Cognition, and Aging at the Conference Psychology and the Brain [Psychologie und Gehirn], Berlin, Germany.

Giroud, N. (2014, September). *Dynamic functional lateralization during speech processing. Developing a paradigm to investigate speech processing in older adults*. Invited talk for the INAPIC Fall Workshop, Zurich, Switzerland.

Invited talks to lab meetings abroad

Giroud, N. (2017 February). *Defining central presbycusis: The relation between brain structure, brain function and behavior in older adults*. Invited Talk at the weekly group meeting of Department of Auditory Neuroscience, Institute of Experimental Medicine, Academy of Sciences in Czech Republic, Prague, Czech Republic.

Giroud, N. (2016, February). *Dynamics of Electrophysiology during Speech Processing and Morphology in Healthy Older Adults*. Invited talk at the group meeting of the National Center for Rehabilitative Auditory Research (NCRAR) at U.S. Department of Veterans Affairs, Portland, USA.

Giroud, N. (2016, February). *The Phonak study: Dynamics of Electrophysiology during Speech Perception in Older Hearing Aid Users*. Invited talk at the group meeting of the Brain and Behavior (B&B) Lab at the University of Washington, Seattle, USA.

Giroud, N. (2016, January). *Dynamics of Electrophysiology during Speech Perception and Morphology in Older Adults with Age-Related Hearing Loss*. Invited talk at the group meeting of the Cognition, Aging, and Psychophysiology (CAP) Lab at Concordia University, Montréal, Canada.

Giroud, N. (2015, October). *Neurophysiology and intervention in adults with age-related hearing loss and hearing aids*. Invited talk at the colloquium of the research unit of Cognitive and Neural Dynamics of Memory at the Max-Planck Institute for Human Development, Berlin, Germany.

Invited talks for a public audience or industry

Giroud, N. (2017, July). *We do not hear with the ear, but with the brain* [Wir hören nicht mit dem Ohr sondern mit dem Hirn]. Invited talk at the Volkshochschule Stäfa, Stäfa, Switzerland.

Giroud, N. (2017, June). *Physical activity, healthy aging, and the brain*. [Fitness, gesundes Altern und das Gehirn]. Invited talk for the annual meeting of the Academic Sports Association Zurich, Zurich, Switzerland.

Giroud, N. (2017, May). *Neuroplasticity in older hearing aid users*. Invited talk to the Schweizerischer Hörakustikerverein. Fribourg, Switzerland.

Giroud, N. (2017, January). *Die Sprache des alternden Gehirns [The Language of the Aging Brain]*. Invited talk for Rotary Club in Bern, Switzerland.

Giroud, N. (2016, May). *Sport & Gehirn [Sport and the brain]*. Invited talk for Swiss Ski Conference organized by Swiss Ski at the Swiss Paraplegic Foundation in Nottwil, Switzerland.

Giroud, N. (2016, April). *Sport & Gehirn [Sport and the brain]*. Invited talk for the semi-annually public lecture "Sport & ..." organized by the Academic Sports Association Zurich at the ETH Zurich, Zurich, Switzerland.

Talks at conferences

Pellegrino, E., He, L., Giroud, N., Meyer, M., & Dellwo, V. (2017, July). *Age-related rhythmic variations: an investigation on Zurich German*. Talk at the 16th Rhythm Production and Perception Workshop, Birmingham, England.

Pellegrino, E., He, L., Giroud, N., Meyer, M., & Dellwo, V. (2017, June). *Rhythmic characteristics in aging: a study on Zurich German*. Talk at the Conference of the Acoustical Society of America, Boston, USA.

Kegel, A., Lai, W.-K., Giroud, N., Meyer, M., & Dillier, N. (2017, February). *Unterschiede in auditorischen Profilen in jüngeren und älteren normalhörenden Erwachsenen*. Talk at the Jahrestagung der Deutschen Gesellschaft für Audiologie, Aachen, Germany.

Giroud, N., Lemke, U., & Meyer, M. (2015, September). *Longitudinal improvement of speech discrimination evidences the efficacy of top-down plasticity as revealed by electrical neuroimaging*. Talk at the International Conference on Basic and Clinical Multimodal Imaging BACI, Utrecht, Netherlands.

Giroud, N. (2015, May). *Cognitive hearing: Neurophysiology and intervention in adults with age-related hearing loss*. Talk at the LIFE Spring Academy, Ann Arbor, USA.

Hasse, A. *, Leemann, A., Giroud, N. *, & Meyer, M. (2014, June). *Entsteht linguistische Salienz im Gehirn?* [Is linguistic salience developed in the brain?] 8th Days of Swiss Linguistics, Zurich, Switzerland.

*authors contributed equally

Poster presentations at conferences

Giroud, N., Hirsiger, S., Kegel, A., Dillier, N., & Meyer, M. (2016, June). *Speaking up does not help older adults with presbycusis to understand – but a thicker cortex does*. Poster at the Organization for Human Brain Mapping, Geneva, Switzerland.

Muri, R., Giroud, N., Hirsiger, S., Kegel, A., Dillier, N., & Meyer, M. (2016, May). *Central hearing loss in healthy aging adults: The contribution of cortical thickness and divided attention to speech perception in noise*. Poster presentation at the Madoko, Zurich, Switzerland.

Bauer, J., Giroud, N., & Meyer, M. (2016, May). *Where are you from? The processing of salient features of Swiss dialects in the brain*. Poster presentation at the Madoko, Zurich, Switzerland.

Kliesch, M., Giroud, N., & Meyer, M. (2016, May). *Learning a new language during old adulthood. A longitudinal study*. Poster presentation at the Madoko, Zurich, Switzerland.

Giroud, N., Lemke, U., & Meyer, M. (2015, December). *Comparing the impact of hearing aid algorithms for neural auditory learning*. Poster at the Workshop Individual differences in language processing across the adult life span: implications for models of comprehension and production, Nijmegen, Netherlands.

Giroud, N., Lemke, U., & Meyer, M. (2015, October). *Longitudinal neural plasticity as a function of using hearing aids with non-linear frequency compression*. Poster at the 6th Aging and Speech Communication Research Conference 2015, Bloomington, USA.

Keller, M., Giroud, N., & Meyer, M. (2015 October). *Auditory alpha power in younger and older listeners during speech prosody processing*. Poster at the 6th Aging and Speech Communication Research Conference 2015, Bloomington, USA.

Giroud, N., Lemke, U., & Meyer, M. (2015, September). *Stabilization neural language functions in healthy older adults using hearing aids with different signal processing algorithms*. Poster at the URPP Dynamics of Healthy Aging Site Visit, Zurich, Switzerland.

Giroud, N., Dellwo, V., & Meyer, M. (2014, October). *Variability of current density in right supratemporal gyrus is related to faster reaction times in auditory prosody task*. Poster presentation at the LIFE Fall Academy 2014 (International Max Planck Research School on the Life Course), Berlin, Germany.

Giroud, N., Dellwo, V., & Meyer, M. (2014, September). *Dynamic functional lateralization during processing of short and long scale intervals in speech signals*. Poster presentation at the conference on auditory cortex, Magdeburg, Germany.

Giroud, N., Keller, M., Kurthen, I., Dellwo, V., & Meyer, M. (2014, May). *The influence of age on speech processing: Testing the paradigm*. Poster presentation at the Limadoko, Zurich, Switzerland.

Kurthen, I., Keller, M., Giroud, N., & Meyer, M. (2014, May). *Elementary speech processing in young adults*. Poster presentation at the Limadoko, Zurich, Switzerland.

Giroud, N., Keller, M., Kurthen, I., Dellwo, V., & Meyer, M. (2014, May). *The influence of age on speech processing: Testing the paradigm*. Poster presentation at the LIFE Spring Academy 2014 (International Max Planck Research School on the Life Course), Charlottesville, USA.

Giroud, N., Keller, M., Kurthen, I., Dellwo, V., & Meyer, M. (2013, October). *Don't let time outrun you: The influence of age on temporal information during speech processing*. Poster presentation at the LIFE Fall Academy 2013 (International Max Planck Research School on the Life Course), Marbach, Germany.

Giroud, N., Keller, M., Kurthen, I., Dellwo, V., & Meyer, M. (2013, September). *Don't let time outrun you: The influence of age on temporal information during speech processing*. Poster presentation at the INAPIC Fall Workshop, Zurich, Switzerland.

Giroud, N., Dellwo, V., & Meyer, M. (2013, September). *Don't let time outrun you: The influence of age on temporal information during speech processing*. Poster presentation at the International Conference on Basic and Clinical Multimodal Imaging BACI, Geneva, Switzerland.

OUTREACH ACTIVITIES

Publications for the public

Benz, E.*, Eicher, S.*, Feld, R. *, Fuchs, B. *, Giroud, N.*, Lehmann, S.*, Mantel, R. *, Martin, M.*, Sonderegger, B.*, Sturm, H.*, Thalmann, W.*, & Wartmann, U.* (2015). *Participatingly developed criteria for good gerontological research* [Parizipativ entwickelte Kriterienliste für gute gerontologische Forschung]. Project description and online publication can be found here: <http://www.zfg.uzh.ch/de/Partizipative-Altersforschung/Downloads-und-Literaturhinweise.html>).

*authors contributed equally

Guye, S. & Giroud, N. (2015). *University Research Priority Program Dynamics of Healthy Aging*. Newsletter article for the LIFE Community (the International Max Planck Research School «The Life Course: Evolutionary and Ontogenetic Dynamics»)

Giroud, N. & Meyer, M. (2016). *Healthy ears, but still suffering from hearing loss?* [Trotz gesunden Ohren im Alter einen Hörverlust erleiden?]. Zeitschrift Dezibel, Dezember 2016.

Media Coverage

- Online article about the research of my dissertation on hearing and aging <http://www.sonova.com/de/features/ hoeren-wird-fuer-das-gehirn-im-alter-anstregender>
- Newsletter of the Academic Sports Association Zurich about my talk on sports and the brain with the title *Sport & the brain: What if brain areas grow by being physically active?* [Sport & Gehirn: Wenn Gehirnnareale mit der Fitness wachsen] <https://asvz.ch/news/59454-sport-gehirn-wenn-gehirnnareale-mit-der-fitness-wachsen>
- Online article about the research of my dissertation on hearing and aging <http://science.orf.at/stories/2798526>

Science fair

Talks for school classes and information desk on neuroplasticity and hearing at the BrainFair Zurich in March 2017: <http://www.brainfair.uzh.ch/de.html>

GENERAL CONTRIBUTIONS TO SCIENCE

10/2016-ongoing	Founder and organizer of interdisciplinary journal club BALi on the (aging) brain and language
01/2015-12/2016	Founder and organizer of peer mentoring group on advanced EEG analyses
10/2014-10/2014	Organizer and moderator of plenary discussion about real-life methods to acquire behavioral and neural data during the LIFE Fall Academy in Berlin
11/2013-06/2014	Fellow Speaker for the International Max Planck Research School „The Life Course: Evolutionary and Ontogenetic Dynamics”

APPROVED RESEARCH PROJECTS

Projects with data acquisition ongoing

10/2016-01/2018	Postdoc in SNF project (nr. 105319_169964). Tasks: planning experiments, publishing research as first and co-author (concerning the PhD student's work), building international collaborations, supervising PhD students
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Projects with data acquisition finished, data analyses ongoing

09/2016-ongoing	Second author of original research article about prosody acquisition in a foreign language, first author Dr. Sandra Schwab (Phonetics Lab) (SNF nr. 148036)
09/2016-ongoing	Co-author of original research article about cognitive effort in language production in Hindi, first author Dr. Sebastian Sauppe (Department of Comparative Linguistics, UZH)
09/2016-ongoing	Second author of original research article about the influence of presbycusis on the processing of vowels in the brain, first author Benjamin Isler (Medical Faculty, UZH)

- 04/2016-ongoing **Co-author** of review article about the relation between language processing and language change, with Prof. Balthasar Bickel, Dr. Sebastian Sauppe, Dr. Damian Blasi (Department of Comparative Linguistics, UZH), Prof. Ina Bornkessel (Australia), Prof. Martin Meyer, Prof. Itziar Laka (Basque Country)
- 03/2015-ongoing **Co-author** of original research article about age-related changes in speech rhythm production, first author Dr. Elisa Pellegrino (Phonetics Lab, UZH)

SUPERVISION OF JUNIOR RESEARCHERS

- PhD theses, ongoing **Benjamin Isler** (Medical Faculty). The influence of presbycusis on the processing of vowels in the brain.
Laura Jagoda. The interaction between cognition and speech perception in tinnitus patients.
Maria Kliesch. Learning a new language during old adulthood. What are the linguistic and cognitive benefits?
Ira Kurthen. Hearing loss and cognition in old age: A fine-grained investigation of speech processing under adverse listening conditions.
- Master theses, ongoing **Shuai Shuao**. Neurocomputational modelling of fMRI data on suprasegmental speech perception.
Alison Schmid. Longitudinal resting-state EEG during adjustment to hearing aids.
- Master theses, 2013-16 **Maria Kliesch** (English Seminar). Neuroplasticity during language learning in older adults.
Julia Bauer. Where are you from? The processing of salient features of Swiss dialects in the brain.
Raphaela Muri. The relationship between auditory acuity and anatomy in the auditory cortex in older adults with mild age-related hearing loss.
Susann Widmer. Age-related differences in the processing of spectral speech information.
Ira Kurthen. Neural processing of rapidly changing cues in the speech signal.
Matthias Keller. The neurofunctional processing of prosodic speech information.
- Interns, 2013-16 **Corina Sager. Anja Betschart. Annina Arquint. Julia Bauer. Florine Bachmann. Jan Juchli. Nora Werner.**
- Matura theses, 2013-16 **Sijamini Baskaralingam. Marika Mitsui.**

ACADEMIC TEACHING

- Spring, 2016 **Bachelor lecture**. (Two lectures). Neuropsychology, University of Fribourg, elective
- Spring, 2016 **Master seminar**. Neurocognition of speech and language, University of Zurich, elective
- Spring, 2015 **Master seminar**. Neuroplasticity across the lifespan, University of Zurich, elective
- Spring, 2015 **Bachelor seminar**. Experimental psychology, University of Zurich, required

Spring, 2014	Doctoral seminar (One workshop). EEG preprocessing, University of Zurich, elective
Spring, 2014	Bachelor seminar. Experimental psychology, University of Zurich, required

REVIEWING AND MEMBERSHIPS

01/2016-ongoing	Reviewing: Plos One, Brain Topography, Cogent Psychology
09/2015-ongoing	Member of The International Society for Brain Electromagnetic Topography ISBET, responsible for Facebook page
08/2016-ongoing	Member of the Society for Human Brain Mapping
07/2015-ongoing	Member of the Association for Psychological Science
01/2014-12/2014	Member of peer mentoring group on applied programming for psychologists
10/2014-05/2015	Member and expert for national youth science competition [Schweizer Jugend forscht]

PRIZES AND AWARDS

01/2016-12/2016	Co-recipient of grant for peer mentoring group (competitive) on EEG data analyses, funded by the Graduate Campus University of Zurich, CHF 9000.-
05/2015-12/2015	Co-recipient of grant for peer mentoring group (competitive) on EEG data analyses, funded by the Graduate Campus University of Zurich, CHF 8500.-
07/2013–06/2015	Grant as principal investigator (competitive) for research project “Neural signatures of speech processing plasticity over the lifespan and benefits of language learning in the elderly”, funded by the Forschungskredit (Candoc) of University of Zurich, CHF 100'050.-
03/2016	Recipient of travel grant for attending the Organizational Human Brain Mapping Conference and Educational Courses in Geneva (CH), funded by the Department of Psychology at the University of Zurich, CHF 1000.-
10/2015	Recipient of student scholarship for attending the 6 th Aging and Speech Communication Research Conference in Bloomington (USA), funded by the conference committee, US Dollars 1000.-
07/2015	Recipient of travel grant for a research visit in the Department of Speech and Hearing Sciences at the University of Washington in Seattle, funded by the Jacobs Foundation, CHF 3791.-
09/2014	Recipient of travel grant for attending the International conference on auditory cortex in Magdeburg (D), funded by the Swiss Academy of Humanities and Social Sciences (SAGW), CHF 400.-
04/2014	Recipient of travel grant for attending the LIFE Spring Academy 2014 (International Max Planck Research School on the Life Course) in Charlottesville (USA), funded by the philosophical faculty of the University of Zurich, CHF 860.-